

4,6-Diaminoisophthalic Acid and Certain of Its De- rivatives

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIRE-
MENTS FOR THE DEGREE OF DOCTOR OF PHILOS-
OPHY IN THE FACULTY OF PURE SCIENCE
OF COLUMBIA UNIVERSITY

BY

ALFRED HEMMER KROPFF, B.S., M.A.,
NEW YORK CITY

1909

EASTON, PA.:
ESCHENBACH PRINTING COMPANY.
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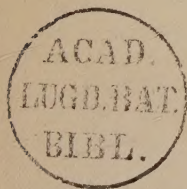
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TO MY FATHER AND MOTHER.

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I wish also to express my thanks to Dr. J. M. Nelson, Dr. A. Hoffman and Dr. K. G. Falk for their interest shown and valuable suggestions offered.

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GENERAL INTRODUCTION.

This dissertation treats of 4,6-diaminoisophthalic acid and of several compounds derived from it by various reactions. The usual derivatives are first described, and then several naphthotetrazines of a new type which were obtained by condensation methods as is further shown herein. In the course of the work several quinazolones were also isolated. They are of a new type, some possessing a carboxyl group in addition to a nitro group on the benzol nucleus, while others have a methyl group in connection with an acetamino group on the benzol nucleus.

4,6-DIAMINOISOPHTHALIC ACID AND ITS DERIVATIVES.

Although twelve possible isomeric diaminophthalic acids can exist, up to 1907, only two have been prepared. These are the 2,5-diaminoterephthalic acid and the 2,5 or 4,5-diaminoisophthalic acid. As yet, not any of the diamino orthophthalic acids, of which there are four possible isomers, have been isolated.

Claus and Wyndham¹ treated isophthalic acid with 5 volumes of fuming nitric acid in a sealed tube at 150–80° for several hours and obtained a dinitro isophthalic acid. This acid, although insoluble in cold water, was soluble in hot water, alcohol, and ether and crystallized in colorless needles which melted at 215°. An analysis showed it to be a dinitro compound. Upon reduction of this acid with tin and hydrochloric acid, the corresponding diaminoisophthalic acid was obtained. This acid was soluble in water to some extent, and could be crystallized from it in flat needles which melted above 300°.

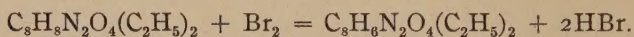
The position of the entering nitro groups, and consequently amino groups was not definitely determined however. When

¹ Claus, Wyndham: J., *prakt* (2), 38, 316.

isophthalic acid is nitrated with fuming nitric acid, a mono-nitro isophthalic acid is obtained which has the nitro group in the 5-position. This much was definitely known. Therefore it is safe to assume that when isophthalic acid is nitrated in a sealed tube with fuming nitric acid, and a dinitro derivative is obtained, one of the nitro groups will also occupy the 5-position. This would make Claus and Wyndham's acid either a 2,5- or a 4,5-diaminoisophthalic acid.

Baeyer in 1886² prepared the diethyl ester of 2,5-diamino terephthalic acid by a totally different reaction from that common in the case of these amino and diaminophthalic acids.

He treated one part of diethyldiimino succinylsuccinate dissolved in twenty parts of sulphuric acid with bromine (1 mol.) according to the following reaction



In the course of a half hour, the free bromine was expelled by means of a current of air, and the solution then poured on ice containing free SO_2 . On treating the precipitated sulphate with sodium acetate, the free diamino terephthalic acid ester was obtained. Later, this same ester was obtained by Häussermann and Martz³ by reducing 2,5-diethyldinitro terephthalate with tin and hydrochloric acid. It has been of especial interest due to the fact that it exhibits dimorphic properties. The same can be said also of ethyl diiminosuccinylsuccinate.

The former exists in a red and a yellow modification, while the latter is found either as a golden yellow compound or as its colorless isomer. Nelson⁴ upon investigation of the ethyl *p*-diaminoterephthalate found that the red form can be changed into a yellow isomeric form upon boiling its alcoholic solution with an alkali salt of a weak acid. And further he found

² Baeyer: *Ber.*, 19, 430.

³ Häussermann, Martz, *Ber.*, 26, 2984.

⁴ Nelson Ph.D., *diss C. U.*, 1907.

that the less stable form can be changed into the more stable form by heating below its melting point.

From these esters the free 2,5-diamino terephthalic acid was obtained⁵ by boiling an alcoholic solution with aqueous alkali, and then acidifying the reaction product with acetic acid. This acid forms in greenish yellow prismatic crystals which are practically infusible, and also insoluble in all indifferent organic solvents.

Nelson⁴ working with the diethyl ester, found that this reacts with phenylisocyanate, forming ethyl *p*-diphenyluraminoterephthalate. This, in turn, condenses with primary amines, as aniline, to form the corresponding naphthotetrazines. Further he found that when 2,5-diaminoterephthalic acid was boiled with acetic anhydride a double ortho condensation took place, forming the corresponding di-lactam of *p*-diacetyldiaminoterephthalic acid. This di-lactam condenses with primary amines to form naphthotetrazines. Ethyl diacetyl diamino terephthalate also condenses with primary amines to form naphthotetrazines or the intermediate amides.

The investigations, as described in this dissertation take up the preparation of another diaminophthalic acid: namely, the 4,6-diaminoisophthalic acid, and also of various compounds derived from it. This acid was obtained from *m*-xylidine by passing through several steps. The base was nitrated at zero degrees, and the corresponding 6-nitro-4-amino-*m*-xylol, which was obtained was reduced by means of tin and hydrochloric acid, yielding the hydrochloride of 4,6-diamino-*m*-xylol. The free diamine was obtained, or its HCl salt was mixed with fused sodium acetate and boiled with acetic anhydride giving the 4,6-diacetyldiamino-*m*-xylol. This compound was then oxidized to the corresponding diacetyl-diamino isophthalic acid by means of potassium permanganate in the presence of magnesium sulphate.

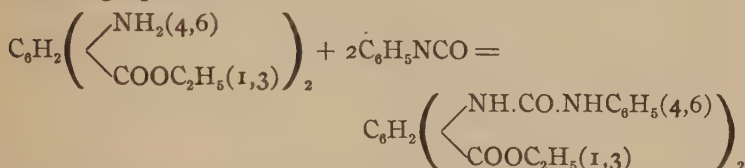
⁵ Böniger, *Ber.*, 21, 1765.

From this acid the free diamino isophthalic acid was readily obtained by saponification of the acetyl group with concentrated hydrochloric acid. The hydrochloride separated out of the acid solution, but, upon being washed with water, hydrolyzed, yielding the free 4,6-diamino isophthalic acid. This acid exists as an amorphous, pinkish powder, which melts with decomposition at about 240° . It is extremely insoluble in all ordinary indifferent organic solvents, and permitted of purification only by repeated solution in dilute alkali and consequent reprecipitation with dilute acetic acid. In this respect it closely resembles the 2,5-diamino terephthalic acid.

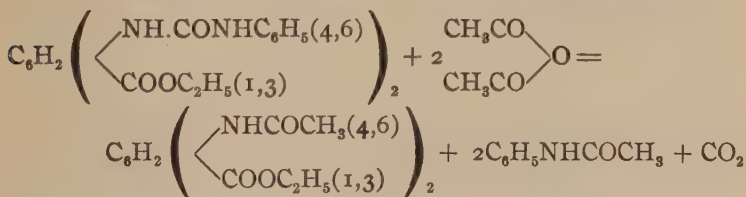
Due, no doubt, to its insolubility, this acid was found to be very unreactive. Acetic anhydride, however, gradually dissolves it with formation first of the corresponding diacetyl diamino derivative, and then the di-lactam of 4,6-diacetyldiamino isophthalic acid. As various attempts to secure condensations with the free acid and other reagents proved unsuccessful, recourse was taken to the esters of this acid. These esters were obtained, although in poor yield, by passing dry hydrochloric acid gas through an absolute alcoholic solution of the diacetyl diamino acid. In this case, saponification of the acetyl group took place at the same time with esterification. The methyl ester forms in beautiful red crystals. As for the ethyl ester, it apparently exists, like the diamino terephthalic ester, in two forms. Usually a light yellow crystalline product was obtained, but it was noticed that after one esterification, a red product was obtained which melted identical with the usual yellow form. This phenomenon, however, was not further studied. As a by-product, a small amount of the acid ester was also obtained. This acid ester melted just about half way between the neutral ester and the free diamino acid, and was also more difficult to obtain in a crystalline form suitable for analysis. Acetic anhydride readily acetylated the neutral esters giving in each case almost

colorless crystalline compounds. Furthermore, the same product was obtained by means of acetyl chloride and the ester in presence of a base like calcium carbonate.

Bogert and Dox⁶ found that ethyl *p*-diamino terephthalate reacts with phenylisocyanate but did not isolate the resulting product to determine its nature. Nelson⁷ found later that phenylisocyanate, even when in excess, gave ethyl *p*-diphenyl uraminoterephthalate. The same is true of ethyl-*m*-diamino-metaphthalate, the reaction taking place as shown by the following equation:



When the above phenyluramino compound was boiled with acetic anhydride, the phenyluramino groups were broken up, obtaining thereby the ethyl-diacetyl-diaminometa-phthalate. This reaction can be expressed by the following equation:



Meyer⁸ has shown that bibasic acids condense with aromatic *p*-diamines, yielding acyl derivatives in which both of the hydrogen atoms of the amino groups have been replaced by the acyl groups. It was found that ethyl *p*-diaminoterephthalate, when fused with phthalic anhydride, gave ethyl *p*-diphthalimido terephthalate. This reaction was accordingly tried

⁶ Bogert and Dox, *J. Am. Chem. Soc.*, **27**, 1127.

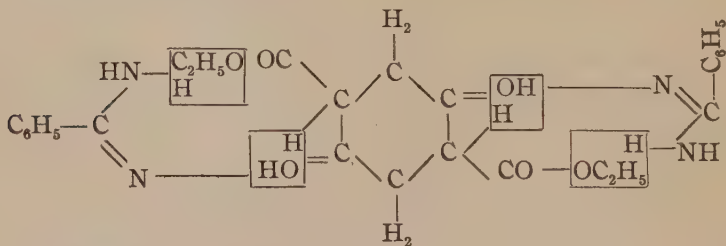
⁷ See 4.

⁸ Meyer, *Ann. der. Chem.*, **347**, 17.

with ethyl-*m*-diamino metaphthalate. It was found that it also takes place in this case giving ethyl *m*-diphthalimido metaphthalate, a compound closely resembling the terephthalate.

When either the methyl or ethyl ester of 4,6-diamino isophthalic acid was dissolved in alcohol and the solution saturated with hydrochloric acid gas, the corresponding hydrochlorides separated in crystalline form. From these hydrochlorides, the free ester was readily re-obtained. In the alcoholic mother liquor after crystallization of the crude product obtained after esterification, another compound was found which has a melting point considerably lower than the metaphthalate. As this compound did not permit of ready purification, it was acetylated, and the corresponding purified acetyl derivative analyzed. This proved to be the ethyl ester of 2,4-diacetyldiamino benzoic acid, the free di-amino acid being formed, no doubt, as a by-product in the esterification of 4,6-diacetyldiaminoisophthalic acid, due to the elimination of one of its carboxyl groups.

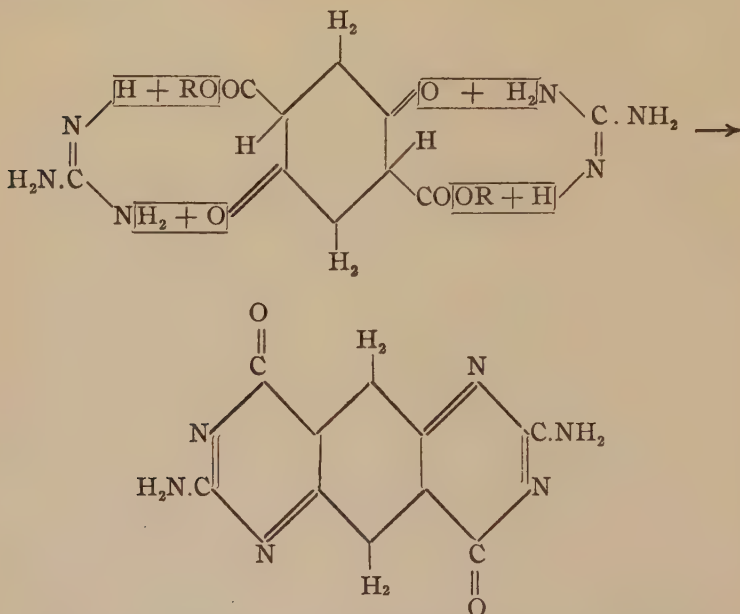
Pinner⁹ in 1889 in connection with some work on the condensation of benzamidine with keto carboxylic esters, obtained from benzamidine and ethyl succinyl succinate a new three-membered heterocycle to which he assigned the name dihydrodiphenyldioxyantetrazine. From the behavior of benzamidine towards ketocarboxylic esters with the formation of pyrimidine derivatives, Pinner represented the reaction as taking place by the following equation:



⁹ Pinner, *Ber.*, 22, 2609.

was independent from that of Pinner. In place of benzamidine, they carried out the condensations between ethyl succinyl succinate and guanidine and also acetamidine.

The reaction taking place in the former case can be shown as follows:



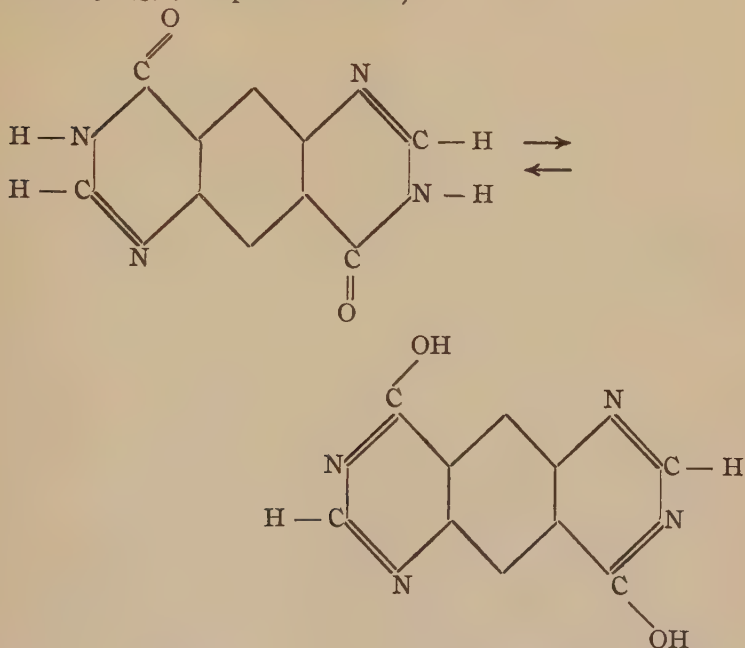
Nelson¹¹ working with ethyl *p*-diaminoterephthalate and some of its derivatives succeeded in making several naphthotetrazines: These he prepared:

- I. By heating ethyl *p*-diamino terephthalate with formamide.
- II. By heating its acetyl derivative with primary amines.
- III. By the action of primary amines upon "diacet dianthranil," and lastly,
- IV. By heating ethyl *p*-diphenyluramino terephthalate with aniline.

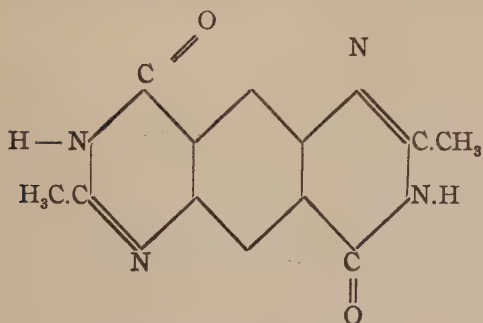
¹¹ See 4.

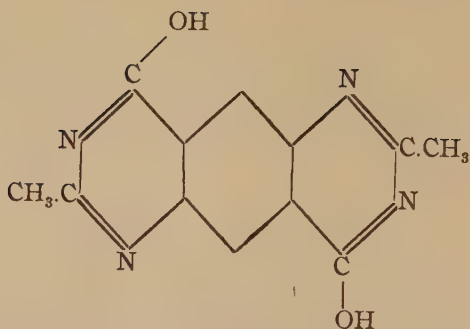
By these various methods Nelson succeeded in preparing the following naphthotetrazines:

I. 4,9 - Diketotetrahydro - 1,3,6,8 - naphthotetrazine (4,9-dihydroxy-1,3,6,8-naphthotetrazine).

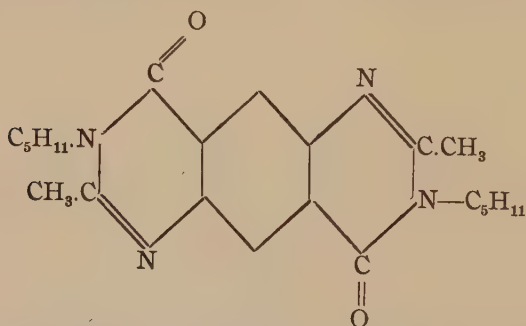


II. 2,7 - Dimethyl-4,9 - diketotetrahydro - 1,3,6,8-naphthotetrazine (2,7-dimethyl 4,9-dihydroxy-1,3,6,8-naphthotetrazine),

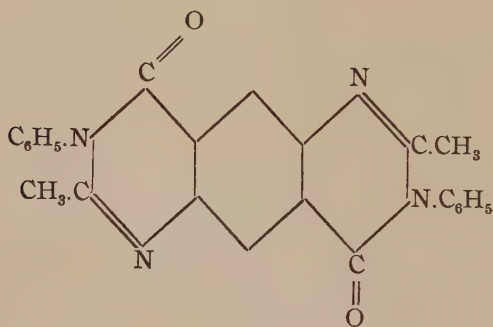




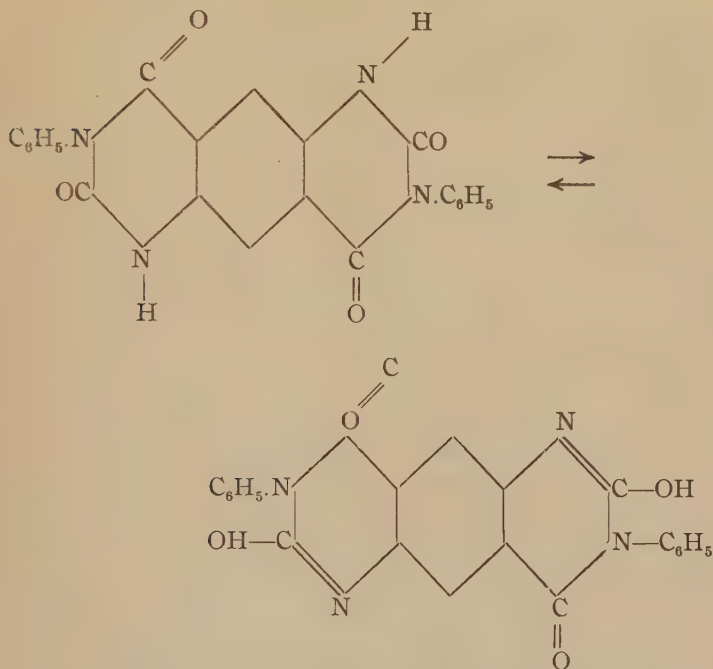
III. 2,7-Dimethyl-3,8-diisoamyl-4,9-diketotetrahydro-1, 3, 6, 8-naphthotetrazine.



IV. 2,7-Dimethyl-3,8-diphenyl-4,9-diketotetrahydro-1,3,6,8-naphthotetrazine,



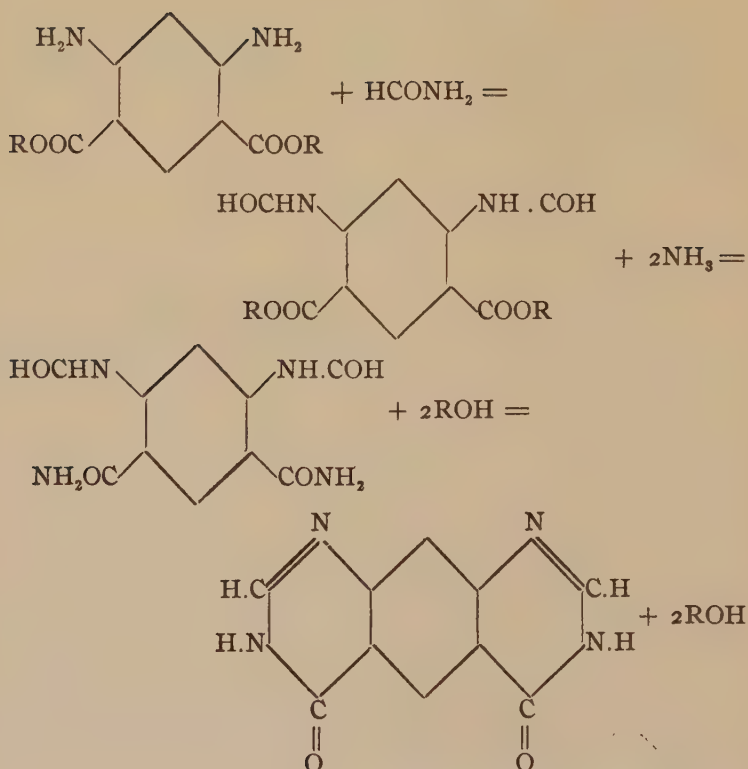
V. 3,8-Diphenyl-2,4,7,9-tetraketoctahydro-1,3,6,8-naphthotetrazine (3,8-Diphenyl-2,7-dihydroxy-4,9-diketotetrahydro-1,3,6,8-naphthotetrazine),



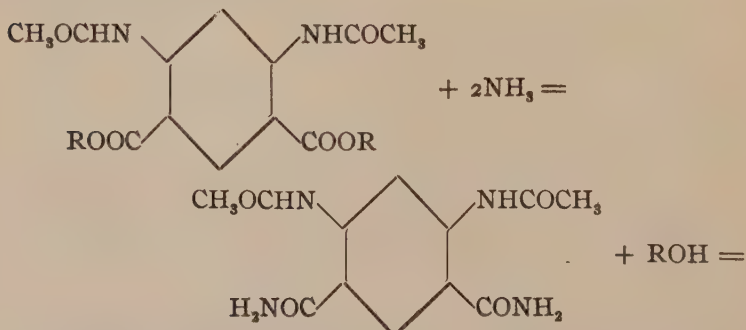
In a similar manner these various reactions were also tried with ethyl-*m*-diaminometaphthalate and some of its derivatives giving rise to a new series of naphthotetrazines in which the two keto groups were in the 4,6-position instead of in the 4,9-position, as was the case in the above compounds. The reactions involved were as follows:

I.¹² Heating ethyl *m*-diaminometaphthalate with formamide:

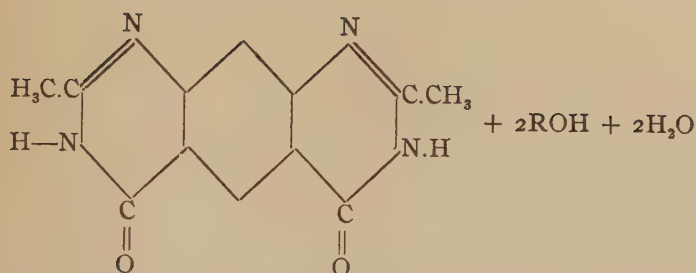
¹² Niementowski, *J. prakt. Chem.* (2), 51, 564. Bogert & Chambers, *J. Am. Chem. Soc.*, 27, 650.



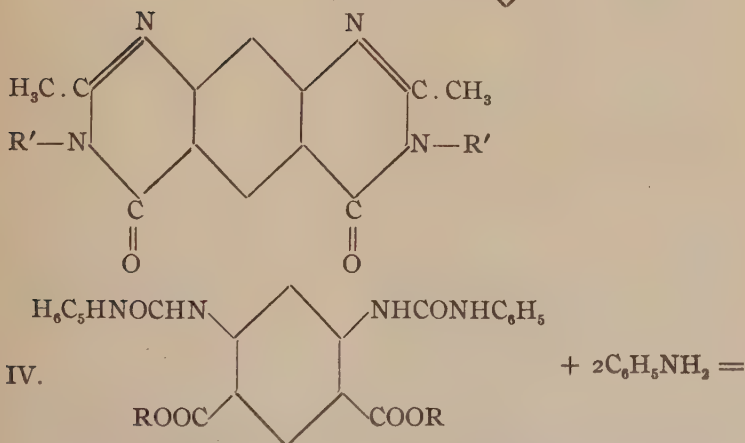
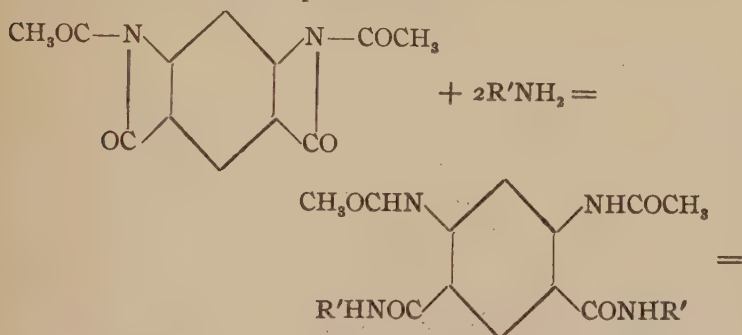
II.¹³ By heating ethyl *m*-diacetyl diamonometaphthalate with alcoholic ammonia:



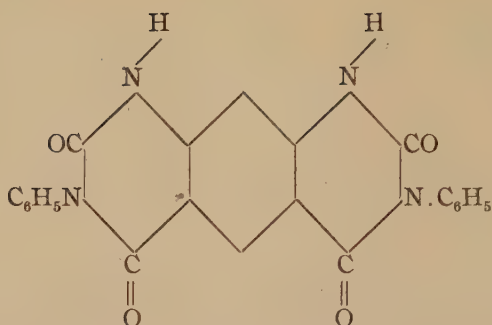
¹³ Weddige, *J. prakt. Chem.* (2), 36, 141; Zacharias, *Ibid.*, 43, 432; Thieme, *Ibid.*, 43, 451.



III.¹⁴ By the action of primary amines upon the dilactam of 4,6-diacetyldiaminoisophthalic acid:



¹⁴Auschütz, Schmidt and Greiffenberg, *Ber.*, 35, 3480; Bogert and Chambers, *J. Am. Chem. Soc.*, 27, 649; Bogert and Seil, *Ibid.*, 27, 1305; 28, 884.



By these various reactions, the following naphthotetrazines were prepared: 4,6-Diketotetrahydro-1,3,7,9-naphthotetrazine (4,6-dihydroxy-1,3,7,9-naphthotetrazine); the 2,8-dimethyl derivatives of the latter; diacetyl-*m*-diaminometa-phthalisoamylamide; 2,8 - dimethyl - 3,7 - diphenyl - 4,6 - di-ketotetrahydro - 1,3,7,9 - naphthotetrazine; 3,7 - diphenyl - 2,4,6,8 - tetraketoctahydro - 1,3,7,9 - naphthotetrazine (3,7 - diphenyl-2-8 - dihydroxy - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine); 2,3,7,8 - tetramethyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine; 2,8 - dimethyl - 3,7 - β - naphthyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine; 2,8 - di-methyl - 3,7 - diamino - 4,6 - diketotetrahydro - 1,3,7,9-naph-thotetrazine; the diacetyl derivative of the latter; and 2,8--dimethyl - 3,7 - diphenylamino - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine, 2,8 - dimethyl - 3-7 - dipropyl (n) - 4,6 - di-ketotetrahydro-1,3,7,9-naphthotetrazine.

In general, these naphthotetrazines are crystalline com-pounds of a high melting point. The majority of those pre-pared are soluble with difficulty or insoluble in the usual or-ganic solvents. Of those investigated so far, the naphtho-tetrazines containing the group



dissolve readily in dilute alkalis and are reprecipitated by dilute acids or by carbon dioxide.

When 4,6-diaminoisophthalic acid was boiled under a reflux condenser with an excess of glacial formic acid, it gradually went into solution, and on cooling very minute crystals of the diformyl derivative separated.

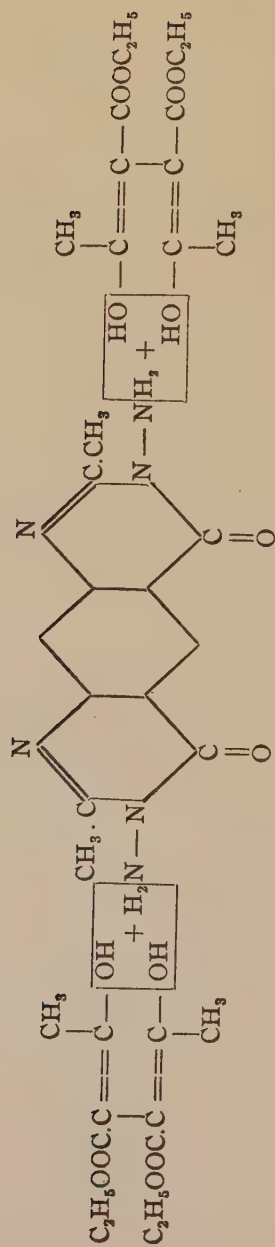
This product is insoluble in water, but soluble in alcohol from which, however, it will not crystallize nicely. It is practically infusible, melting only when the capillary tube was held directly in the flame of the Bunsen burner. It was hoped, that by boiling this diformyl derivative with acetic anhydride, the latter reagent would act as a dehydrating agent, yielding a "diformyl anthranil," but this was not the case, "diacetanthranil" being formed instead. The acid was then neutralized with ammonia and taken to dryness on the water bath, and the ammonium salt heated in an oil bath at 200° for an hour, with the anticipation that the ammonium salt would dehydrate with formation of the same naphthotetrazine as was obtained by heating ethyl-*m*-diaminometaphthalate with formamide.

Decomposition, however, took place, and no formation of any tetrazine was apparent.

Bülow,¹⁵ and Bülow and Weidlich,¹⁶ have shown that compounds containing an $>N-NH_2$ group condense with diacetosuccinic diethyl ester to form corresponding pyrrole derivatives. Accordingly, the naphthotetrazine obtained by action of hydrazine hydrate upon the diacetanthranil was condensed with diaceto succinic ester. In this case two $>N.NH_2$ groups were present. The reaction taking place as follows:

¹⁵ Bülow, *Ber.*, **39**, 2621-2.

¹⁶ Bülow & Weidlich, **39**, 3372-77.



It was found necessary, however, to boil the naphthotetrazine direct with benzaldehyde in order to get a reaction. The compound then formed, was yellow and granular, and insoluble in alcohol, ether, acetone and the other usual solvents.

When the diamino naphthotetrazine was dissolved in dilute hydrochloric acid and treated with NaNO_2 and immediately thrown into an alkaline solution of α - or β -naphthol a deep red dye was formed. When, however, the naphthotetrazine was allowed to stand a few minutes after the treatment with nitrous acid and before adding to the naphthol, no evidence of a dyestuff was apparent. This is due no doubt to the breaking up of an unstable compound in solution, as a decided evolution of nitrogen was observed.

Acetic anhydride reacts with the diamino naphthotetrazine giving a diacetyl derivative. No evidence of the formation of any tetra-acetyl compound was observed. Further action of acetic anhydride on the diacetyl diamino naphthotetrazine likewise did not produce any of the tetra-acetyl derivative.

As a by-product in the oxidation of 4,6-diacetylxylylene diamine to the corresponding isophthalic acid, 4,6-diacetaminometatoluic acid was also obtained. This formation was usually noticed when the oxidation was carried on in a flask under a reflux condenser, and then only small quantities were obtained. Later, it was attempted to prepare this toluic acid directly from the diacetylxylylenediamine by adding a slight excess over the calculated amount of potassium permanganate necessary to oxidize only one of the methyl groups of the diamine. It was found, however, that the oxidation is not partial, but complete, giving the 4,6-diacetyldiaminoisophthalic acid and a considerable amount of unchanged starting material. Only a very small quantity of the diacetyldiaminotoluic acid could be isolated.

Acetic anhydride converts this acid to the corresponding anthranil. Peculiarly enough, this anthranil crystallizes from acetic anhydride with one-half molecule of acetic acid. This

can hardly be called acetic acid of crystallization, as it remains in the compound even when kept at a temperature of 120° C. for several hours. It might be called "acetic acid of constitution" more readily. That this really is the case was shown by gently heating some of the anthranil in a test tube over a free flame until it melted. The odor of acetic acid was very apparent, and blue litmus held over the top of the tube was also instantly reddened.

Ammonia and aniline readily condensed with this anthranil giving quinazolines which had both a methyl and an acetamino group on the benzol nucleus. Dilute alkali readily saponified this acetamino group, yielding the free C-aminoquinazoline. Nitrous acid diazotized this amino group, and the diazo compound in solution then gave an orange dye when coupled with α -naphthol.

Errera and Maltese¹⁸ have already prepared the 4-amino-6-nitroisophthalic acid by oxidation of the 4-acetamino-6-nitrometaxylol with potassium permanganate. It was found that a better yield of this acid could be obtained when magnesium sulphate was added in the oxidation to preserve a neutral reaction. Dilute sulphuric acid saponifies this acid, giving the free 4-amino-6-nitroisophthalic acid. When, however, stronger sulphuric acid was used in saponification, CO_2 split out at the same time, giving a mixture of 4-nitroanthranilic acid and 2-nitro-4-aminobenzoic acid.

This latter acid was also prepared in the ordinary method employed in obtaining such compounds. Paratoluidine was nitrated with a mixture of concentrated nitric and sulphuric acids below 0° C. exactly as described by Nölting and Collin.¹⁹ The resulting 2-nitro-*p*-toluidine was acetylated and the methyl group oxidized to carboxyl by potassium permanganate, giving 2-nitro-4-acetaminobenzoic acid. The acetyl group was then eliminated by means of dilute sulphuric

¹⁸ Errera and Maltese, *Gazz. chim. ital.*, **33**, 287.

¹⁹ Nölting and Collin, *Ber.*, **17**, 263.

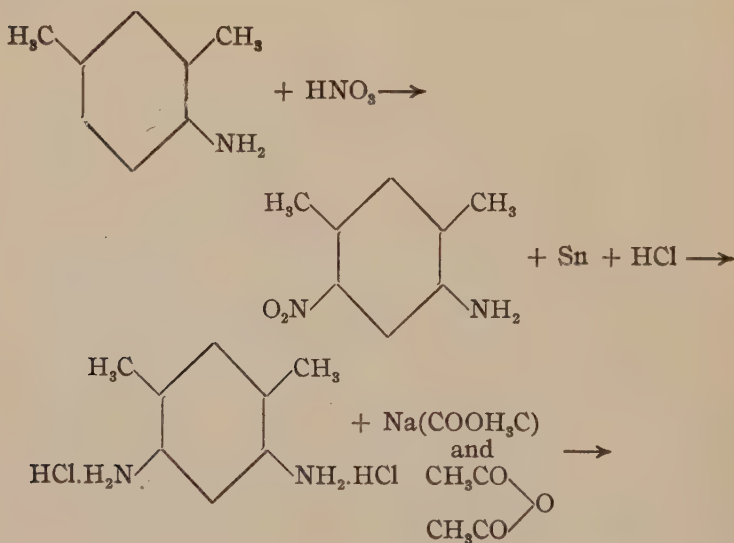
acid or 10 per cent. caustic potash solution, giving rise to the free amino acid. This acid, and also its acetyl derivative, melted at the same temperature as the acid obtained above from saponification of the 4-amino-6-nitroisophthalic acid with strong sulphuric acid and its corresponding acetyl derivative.

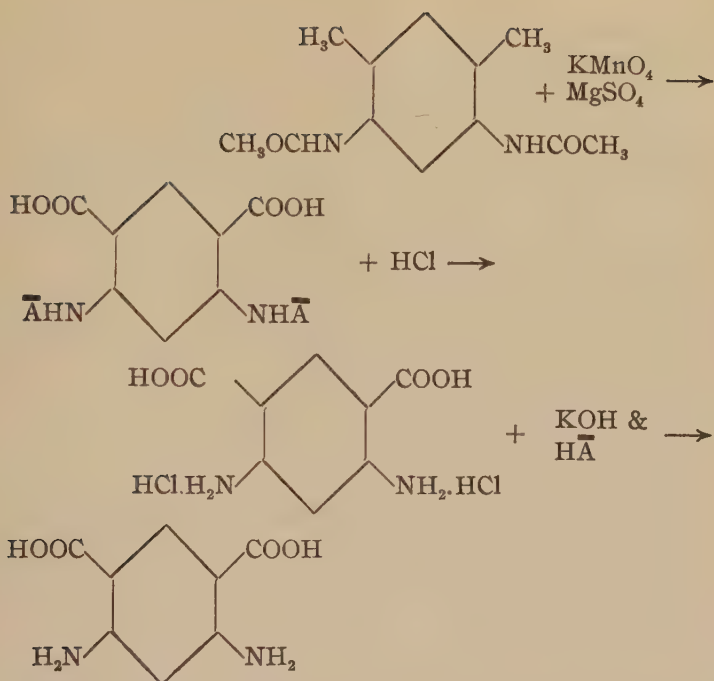
When the 4-amino-6-nitroisophthalic acid was boiled for some time with an excess of acetic anhydride, the corresponding anthranil was formed. This anthranil possesses a nitro and a carboxyl group on the benzene nucleus. Ammonia and primary amines acted upon this anthranil in the usual manner, giving rise to a new series of quinazoline compounds.

EXPERIMENTAL PART.

4,6-Diaminoisophthalic Acid and Some of Its Derivatives.

Preparation of 4,6-Diaminoisophthalic Acid.—The steps in the preparation of this acid are illustrated graphically as follows:





As can be seen from the above, the starting material was 1,3,4-*m*-xylidine. When this compound is treated with a mixture of concentrated nitric and sulphuric acids in the cold, two isomeric mononitro-*m*-xylidines are formed, namely, the 2-nitroxylidine and the 6-nitroxylidine. The former melts at about 80° and the latter at 123°. The lower the temperature, the less of the low melting isomer will be formed.

In preparing 6-nitroxylidine the method given by Nölting and Colin²⁰ was employed. 1,3,4-*m*-Xylidine was dissolved in eight parts of concentrated sulphuric acid, and the mixture cooled to 0° C. by means of ice and salt. Then the calculated amount of nitric acid was mixed with two parts by weight of concentrated sulphuric acid and this mixture also

cooled to 0°C . The acid mixture was then allowed to drop slowly into the xylydine solution, care being taken that the temperature did not rise at any time above 2°C . By using a mechanical stirrer, and allowing the acid to run through a coil surrounded by ice and salt before it reached the xylydine-sulphuric acid mixture, it was found that the nitration proceeded smoothly and no difficulty was experienced in keeping the temperature around 0°C .

In this way, 250 grams of *m*-xylydine were nitrated in about $3\frac{1}{2}$ hours. After all of the acid had been added, the reaction product was allowed to reach the room temperature and then was poured into a large amount of ice-water. This solution was then neutralized with dry soda. This precipitated the crude nitro compound, which was filtered on a large Büchner funnel, washed thoroughly and crystallized from alcohol in which it was quite soluble. 6-Nitroxylydine forms in large, well-defined, red crystals which melt at 123°C . One crystallization of the crude nitro compound was found sufficient to separate it completely from any 2-nitroxylydine formed in the nitration. The 6-nitroxylydine was also prepared by passing ammonia gas and hydrogen sulphide into an alcoholic solution of 4,6-dinitro-*m*-xylol, as was first shown by Grevink.²¹ The yield of pure nitroxylydine in this case, however, is not very good.

Hydrochloride of 4,6-Diamino-m-xylol,



This compound was readily obtained from the 6-nitroxylydine by reduction with tin and hydrochloric acid. It had already been prepared by Luhmann and by Grevink. Ten grams of the nitro compound and 14 grams of granulated

tin were put together in an Erlenmeyer flask and 25 cc. of conc. HCl added. In a few minutes the mixture became warm, and hydrogen was evolved. If the reaction became too violent, the flask was immersed in cold water for a short time. Twenty-five cc. of conc. HCl were again added and the mixture boiled over a free flame until almost all of the HCl had been driven off. About 700 cc. of water were then added, and a rapid stream of H_2S allowed to pass through the solution. The stannic sulphide was filtered off and H_2S again passed through the solution to remove the last traces of tin. After again filtering, a clear, colorless solution was obtained. This was concentrated strongly in a casserole, and a large excess of conc. HCl added. On cooling, crystals of the hydrochloride of 4,6-diamino-*m*-xylol separated out. These were filtered off, washed with conc. HCl and dried. To all appearances this compound corresponded to the product previously obtained by Luhmann and by Grevingk.

4,6-Diacetyldiamino-m-xylol,



This compound was obtained from the above hydrochloride by boiling the same with acetic anhydride in the presence of a calculated amount of fused sodium acetate to take care of the hydrochloric acid. After boiling for about an hour, at the end of which time the residue in the flask appeared to be only sodium chloride, the reaction product was poured into water and boiled to expel the excess of acetic acid. During the boiling, large glassy-like crystals of the di-acetyl derivative separated. The solution was then cooled and filtered. The crystals melted at 295.2° (corr.). They are soluble in

glacial acetic acid, from which they recrystallize nicely. They are less readily soluble in alcohol. Later on in the work it was found that this same acetyl derivative was obtained more readily by adding caustic alkali to the solution of the hydrochloride until slightly alkaline, reacidifying with acetic acid and adding a slight excess over the calculated amount of acetic anhydride direct. Considerable heat was developed, and the diacetyl derivative crystallized out in a pure state. The mother-liquor, on concentration and another addition of acetic anhydride, yielded another crop of crystals. When the diacetyl derivative is boiled for a short time with conc. HCl, the acet group is split off, and on cooling the hydrochloride of 4,6-diamino-*m*-xylol is again formed.

4,6-Diacetyldiaminoisophthalic Acid,



This acid was readily obtained when the above diacetyl derivative was oxidized with KMnO_4 in the presence of MgSO_4 to keep the reaction neutral. The oxidation was carried out in a large evaporating dish by means of a current of steam. Twenty grams of diacetyldiamino-*m*-xylol and 40 grams of MgSO_4 were put into an evaporating dish, three liters of water added, and the whole heated to boiling. Steam was then introduced, and 60 grams of powdered KMnO_4 gradually added. After all the KMnO_4 had been added, steam was continued to be passed through the solution until all the color of the KMnO_4 had disappeared. The total oxidation usually took about 2 hours. The hot solution was then filtered by suction from the MnO_2 and again heated to boiling in a dish. Portions of about 800 cc. were drawn off and acidified with

HCl. A copious, somewhat gelatinous precipitate formed which was filtered by suction and washed to free it from HCl. This precipitate was separated from the paper and dried at 110° .

It is practically pure 4,6-diacetyldiaminoisophthalic acid. This acid can be crystallized from acetic acid, or better, from alcohol. It forms in long white needles, which melt at $276^{\circ}.2$ (corr.). It is fairly soluble in acetic acid, much less so in alcohol, from which it crystallizes nicely, and almost insoluble in benzol, ether or chloroform. It is readily soluble in alkalis, and is reprecipitated in a gelatinous form by HCl. A Dumas nitrogen determination showed 10.2 per cent. N.

Calculated for
 $C_{12}H_{13}O_6N_2$
Per cent.
10.00

Found.
Per cent.
10.2

Hydrochloride of 4,6-Diaminoisophthalic Acid,



When 4,6-diacetyldiaminoisophthalic acid was boiled for some time with conc. HCl, solution suddenly took place, and almost immediately yellowish needles of the hydrochloride of 4,6-diamino acid separated out. These were filtered, washed with conc. HCl and dried. They gave a melting point of 229° – 230° (corr.).

This hydrochloride, when put into water, undergoes a change. The crystals become opaque and powdery, and hydrolysis takes place, forming 4,6-diaminoisophthalic acid.

4,6-Diaminoisophthalic Acid,

This acid was obtained by dissolving the above hydrochloride in dilute KOH solution, filtering to get rid of a small amount of impurities, and acidifying the solution with dilute acetic acid. It is precipitated as a pinkish, amorphous powder, which, when dry, melts at 235° (corr.) with decomposition. The acid is insoluble in all organic solvents. Alcohol, ether, benzol, chloroform, amyl acetate, etc., were all tried as solvents without success. Apparently the only method of purification was to repeatedly dissolve the acid in caustic alkali and reprecipitate with acetic acid. It then finally appeared as a pinkish powder. This acid is very unreactive. Although it might be regarded as a double anthranilic acid, it failed to give any reactions common to the latter. It will not, for example, condense with chloracetic acid to give a double phenylglycine-*o*-carbonic acid. Fusions with urea failed to give a double benzoylene urea. A fusion with formamide failed to give the desired naphthotetrazine, although this was later obtained by the action of formamide upon the diethyl ester of the diamino acid. Esters could not be prepared from the free diamino acid; recourse to the diacetyl derivative had to be taken. Boiling with concentrated hydrochloric acid failed to reform the hydrochloride. Glacial formic acid in large excess, however, gradually dissolves the acid with formation of the diformyl derivative. Acetic anhydride first forms diacetdiaminoisophthalic acid and then the excess of acetic anhydride acts as a dehydrating agent with formation of "di-acetanthraniol." An alkaline solution of the diamino acid is somewhat fluorescent. The acid itself

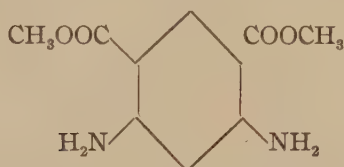
exhibits tribo-electric properties. Attempts were also made to diazotize the two amino groups of the acid in the hope of obtaining a diazo compound which, on boiling with water, would yield a 4,6-dihydroxyisophthalic acid or rather a "resorcin dicarbonic acid." The latter reaction, however, did not take place, owing to the position of the amino group. Instead, colored compounds, analogous to Bismarck browns, were obtained. These were not further studied.

Upon analysis, the following results were obtained:

C = 49.13 per cent; H = 4.4 per cent.; N = 14.4 per cent.

Calculated for $C_8H_8O_4N_2$; —C = 48.99 per cent.; H = 4.1 per cent.; N = 14.28 per cent.

Dimethyl-m-diaminometaaphthalate,



As has already been stated, it was found that the diamino acid could not be esterified, due probably to its insolubility in alcohol. When, however, dry hydrochloric acid gas was allowed to pass through a hot alcoholic solution of the diacetyldiaminoisophthalic acid for several hours, the color of the solution gradually changed from practically colorless to a deep yellow, and esterification took place. It was observed that saponification took place at the same time, there being a distinct odor of ethyl acetate apparent. In detail, the method of preparation of the methyl ester is as follows: Five grams of diacetyldiamino acid were put into a flask with about 200 grams of absolute methyl alcohol, and the mixture heated on the water-bath under a reflux condenser. Dry hydrochloric acid gas was then bubbled through the solution. The diacetyldiaminoisophthalic acid gradually went into solu-

tion, and the liquid became light yellow. After about two hours the color had changed to a deep reddish-yellow, and no more diacetyl acid was apparent. Upon continued action of the hydrochloric acid gas, reddish needle-like crystals, which proved to be the hydrochloride of the ester, separated out of the hot alcoholic solution. At this point the process was stopped, and the solution cooled and filtered. The alcohol was now distilled off on a water-bath under diminished pressure. The distillation was interrupted several times and the crystals which had formed on concentrating the solution were filtered off. When almost all of the alcohol had been driven off, water was added to the residue remaining in the flask. The crystals of the hydrochloride of the ester obtained during the various stages of esterification and distillation were also put into the flask and dry sodium carbonate added until all effervescence had ceased, and the solution had a slight alkaline reaction. The red, amorphous residue was filtered and dissolved in the least amount of boiling alcohol. On cooling, beautiful red, needle-like crystals were obtained which gave a melting-point of $204^{\circ}.6$ (corr.). On acidification of the alkaline filtrate with acetic acid, a yellowish precipitate formed which was filtered off and extracted with boiling alcohol several times. This left a slightly yellow residue which melted at about $235^{\circ}.6$ (uncorr.) and apparently was some diamino acid formed by saponification of the diacetyldiaminoisophthalic acid.

A Dumas nitrogen determination was made on the red crystals with the following results:

0.15 gram substance gave 16.4 cc. of nitrogen at 19° and 764 mm. pressure.

N calculated for the dimethyl ester of 4,6-diaminoisophthalic acid ($C_{10}H_{12}O_4N_2$) = 12.5 per cent. Found, N = 12.64 per cent.

Upon saponification with caustic potash solution and then acidification with acetic acid, the desired diaminoisophthalic

acid was obtained. The presence of any acid ester was not noticed. The alcoholic solution of the ester possesses a decided fluorescence.

Hydrochloride of Dimethyl-m-diaminometa^{phthalate},



Dry HCl gas was passed through an alcoholic solution of the dimethyl ester. In a few minutes a heavy precipitation of the desired hydrochloride occurred. The hydrochloride is thrown down in a crystalline form as shiny needles. It is practically insoluble in alcohol and melts at $235^{\circ}.5$ (corr.) with evolution of gas. A dilute solution of sodium carbonate when added to a small portion of the hydrochloride caused effervescence and reformation of the free ester.

Dimethyl-m-diacetyldiaminometa^{phthalate},



When the dimethyl ester of 4,6-diaminoisophthalic acid was boiled for a few minutes with a slight excess of acetic anhydride, it gradually dissolved, forming a clear reddish-colored solution. This was poured into a large excess of water and thoroughly agitated until all of the acetic anhydride had mixed with the water. A white amorphous substance was thrown out of solution. This was filtered, washed to free it from acetic acid, and crystallized from methyl alcohol, in which it is fairly soluble. The diacetyl compound

formed in nice, long, colorless needles, melting sharply at 256° (corr.). A nitrogen analysis gave the following result:

0.1520 gram of substance gave 12.3 cc. of nitrogen at 19° and 754 mm. pressure.

	Calculated for $C_{14}H_{16}N_2O_6$ Per cent.	Found. Per cent.
N	9.09	9.22

Diethyl Ester of 4,6-Diaminoisophthalic Acid,



This ester was made in the same manner as has already been described under the preparation of the dimethyl ester. It was found that the yield of pure ester, although poor under the best conditions, was best when absolute ethyl alcohol was used. The diethyl ester crystallizes from dilute alcohol in long yellowish needles which melt at 169° (corr.).

Apparently a dimorphic condition exists here, as in the case of the diethyl ester of 2,5-diaminoterephthalic acid. One crop of crystals obtained had a distinct red color, but otherwise were identical with the yellow modification. All attempts to again prepare the red isomer were fruitless. Apparently the yellowish crystals are the stable modification. When saponified with KOH, the diethyl ester, just like the dimethyl compound, gives the free diaminoisophthalic acid. Unlike the acid, however, the ester proved to be much more reactive in forming condensations with other reagents. It condensed, for example, with formamide, yielding an almost quantitative yield of the desired naphthotetrazine. Phenylisocyanate reacted with the diethyl ester to form ethyl diphenyluraminometaphthalate, which in turn yielded the

naphthotetrazine when heated with aniline. The ester is insoluble in water, easily soluble in ethyl or methyl alcohol, and fairly soluble in benzol. It is insoluble in chloroform, gasolene or ligroin. The alcoholic solution, as in the case of the dimethyl ester, is strongly fluorescent.

A Dumas nitrogen determination gave the following results:

Wt. of sample, 0.15 grams. Volume of N = 14.9 cc.; T = 21°; P = 762 mm.

	Calculated for $C_{12}H_{16}N_2O_4$ Per cent.	Found Per cent.
N	11.11	11.34

Hydrochloride of Diethyl Ester of 4,6-Diaminoisophthalic Acid,



This hydrochloride was obtained by saturating an alcoholic solution of the diethyl ester with HCl gas. It formed in fine needles of slight yellowish color. M. p. = 245°.4 (corr.). Like the hydrochloride of the dimethyl ester, it is insoluble in alcohol and is decomposed by sodium carbonate solution into the free ester.

Diethyl-m-diacetylaminometaphthalate,



This diacetyl compound was readily obtained when the diethyl ester was boiled for a few minutes with an excess of

acetic anhydride and the reaction product poured into water. The desired compound which separated out as an amorphous solid was filtered, washed and dissolved in alcohol, from which it crystallized on cooling in slightly yellow-colored needles, melting at $230^{\circ}.4$ (corr.).

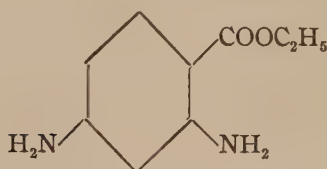
The pure compound possesses a fluorescence and is soluble in alcohol, benzol, and most of the ordinary organic solvents. The same compound is also obtained by heating the diethyldiamino ester with acetyl chloride. In this case a little calcium carbonate was added to take care of the hydrochloric acid formed in the reaction.

A nitrogen analysis of the product gave the following result:

Wt. of sample = 0.15 grams. cc. of N = 11.6. T = 23° .
P = 747 mm.

	Calculated for $C_{15}H_{20}O_6N_2$	Found Per cent.
N	8.33	8.56

Ethyl ester of 2,4-Diaminobenzoic Acid,



Upon concentration of the alcoholic mother-liquor obtained in crystallizing the crude products from the esterification of the diacetyldiamino acid with ethyl alcohol, a reddish, pulverulent product was obtained which melted at about 102° . As this product was very soluble in even dilute alcohol and would not crystallize it was found difficult to prepare it in a condition suitable for analysis. Under the assumption that it probably was an ester of 2,4-diaminobenzoic acid formed by elimination of one carboxyl group from the diacetyl-

diaminoisophthalic acid during esterification, it was acetylated in the hope of being able to get a product which would permit of better purification. It was also attempted to saponify the ester with dilute caustic potash solution in the hope of obtaining the free 2,4-diaminobenzoic acid, which already had been prepared in a different manner by Ullmann and Uzbachian.²² As this acid, however, is apparently a very unstable combination, losing its carboxyl group readily, these attempts were unsuccessful. No free acid could be isolated and when the alkaline liquid, after saponification, was extracted with ether and the mixture dried and the solvent subsequently evaporated, a dark-colored oily mass was left in the vessel, indicating that it probably was very impure metaphenylenediamine.

Ethyl 2,4-Diacetyldiaminobenzoate,



The above ester was treated with an excess of acetic anhydride. Immediate solution with formation of considerable heat took place. After boiling a short time to ensure complete acetylation the reaction product was poured into water and boiled. Upon cooling a slightly yellow-colored compound crystallized out in groups of small needles. This was filtered from the acid liquor and recrystallized from water. The pure compound is yellowish white, and melts at $189^{\circ}.4$ (corr.). It is easily soluble in alcohol, benzol and other organic solvents and crystallizes best from water. A Dumas nitrogen analysis gave the following figures:

0.15 gram of sample gave 14.6 cc. of N at 23° and 758 mm.

²² Ullman and Uzbachian, *Ber.*, 36, 1802.

N	Calculated for	Found.
	$C_{13}H_{16}O_4N_2$ Per cent.	Per cent.
	10.6	10.9

Monoethyl ester of 4,6-Diaminoisophthalic Acid.



When the alkaline aqueous mother-liquor obtained after removing the crude diethyldiamino ester was acidified with acetic acid a yellowish amorphous precipitate was formed. This was filtered off, washed with water and boiled with alcohol. In this way the acid ester formed was separated from diamino acid, which also was present, as the latter compound is insoluble in alcohol. Upon concentration of the alcoholic solution a yellowish crystalline compound separated out, which melted at $211^{\circ}.6$ (corr.) with decomposition. This compound is soluble in a solution of sodium carbonate or caustic potash, from which it is reprecipitated upon acidification with acetic or hydrochloric acids. It is easily soluble in alcohol, from which it crystallizes in short flat prisms of a yellowish-red color. Upon analysis the following figures were obtained:

0.1507 gram of substance gave 16 cc. of N at 13° and 770 mm.

N	Calculated for	Found.
	$C_{10}H_{12}O_4N_2$ Per cent.	Per cent.
	12.5	12.65

Ethyl diphenyluraminometaphthalate,



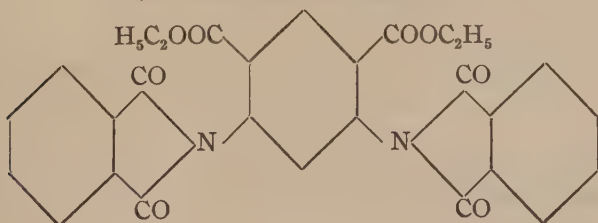
Three grams (1 mol.) of ethyl diaminometaphthalate were dissolved in about 60 cc. of benzol in a flask to which a reflux condenser was attached and placed on a steam-bath and 2.83 grams (2 mols.) of phenylisocyanate added to the clear solution. The benzol had previously been dried by allowing it to stand over sodium. This precaution was taken so that none of the phenylisocyanate might be decomposed by moisture. It was afterwards found that this precaution was unnecessary, as an excess of the isocyanate did not affect the results, and also as the diphenylurea which would be formed is easily soluble, whereas the phenyluramino compound is insoluble. After heating for about $1\frac{1}{2}$ hours the solution was cooled and the crystals were separated out, filtered and washed with dry benzene and then with hot alcohol, dried at 110° to constant weight, and analyzed with the following results:

0.15 gram of sample gave 15.6 cc. of N at 22° .5 and 760 mm.

	Calculated for $C_{26}H_{26}O_6N_4$ Per cent.	Found. Per cent.
N	11.47	11.7

The pure phenyluramino derivative is a white crystalline solid forming in nice large needles and melting at 256° .8 (corr.). It is insoluble or very difficultly soluble in water, alcohol, carbon tetrachloride and ethyl acetate. When the phenyluramino derivative is heated with aniline, a naphthotetrazine is formed which will be described later.

Ethyl-m-diphthalimidoisophthalate,



Ethyl-*m*-diaminoisophthalate was fused with an excess of phthalic anhydride, and the claret-colored melt, when cold, extracted repeatedly with boiling alcohol to remove all excess of the anhydride. A cream-colored residue remained which was crystalline in structure and melted at $251^{\circ}.8$ (corr.). This residue is apparently insoluble in benzol, toluol or chloroform. A Dumas nitrogen determination showed the following:

Wt. of sample — 0.15 gram. No. of cc. of nitrogen = 7.6.
 $T = 23^{\circ}$. $P = 761$ mm.

	Calculated for $C_{28}H_{20}O_8N_4$. Per cent.	Found. Per cent.
N	5.47	5.71

Dilactam of m-Diacetyldiaminometaaphthalic Acid.



When 4,6-diaminoisophthalic acid was boiled for some time under a reflux condenser with a considerable excess of acetic anhydride, it gradually went into solution with formation of a dark-colored liquid. Upon cooling, long white needles crystallized out in copious quantities. These were filtered, washed with acetic anhydride and finally with gasolene to remove the excess of anhydride.

These crystals matted down on the filter, forming a snow-white compound which resembled cotton. They melted at $282.^{\circ}3$ (corr.). A nitrogen analysis gave the following results:

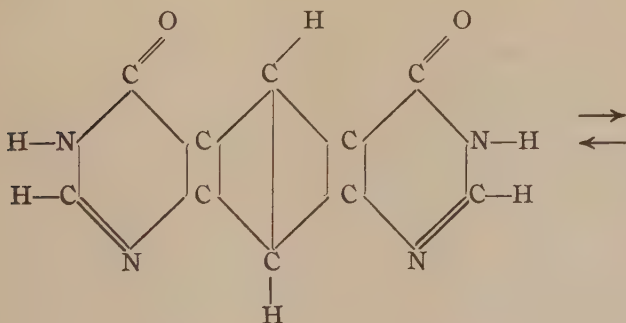
0.151 gram of substance dried to constant weight gave 15.4 cc. of nitrogen at 21° and 764 mm.

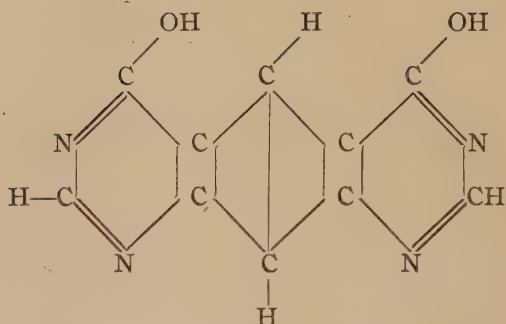
N	Calculated for	Found.
	$C_{12}H_8O_4N_2$. Per cent.	Per cent.
	11.47	11.6

This same compound was obtained when 4,6-diacetyldiaminoisophthalic acid was boiled with an excess of acetic anhydride. In the case of the diamino acid, acetylation of the amino group probably first took place, and then the excess of acetic anhydride acted as a dehydrating agent, eliminating two molecules of water with formation of the "diacetanthranil." When boiled with a large excess of water, the compound gradually changed, with formation of 4,6-diacetyldiaminoisophthalic acid. In general, it was found that this compound behaved like "acet-anthranil," condensing with ammonia and primary amines to form naphthotetrazines (literally "double quinazolines"). For convenience, this dilactam is called "Diacetanthranil" in the experiments which follow.

The compound is soluble in alcohol, giving the diacetyldiamino acid, but can be crystallized from ethyl acetate, or best, acetic anhydride, without undergoing any change.

4,6-Diketotetrahydro-1,3,7,9-naphthotetrazine (*4,6-Dihydroxy-1,3,7,9-naphthotetrazine*).





Note: The numbering of the nucleus as given in Richter's "Lexikon" has been adopted throughout in the naming of these naphthotetrazines.

Ethyl-*m*-diaminometaphthalate (1 molecule) and formamide (2 molecules and slight excess) were allowed to react in a sealed tube for about seven hours at 200° – 210° .

The excess of formamide was used in the hope that it might act as a solvent. Such was not the case, however.

At the close of the reaction, the tube contained a dark-colored solid. Upon opening considerable pressure was evident in the tube. The mass was treated with dilute potassium hydroxide, in which it dissolved readily, and boiled until all odor of ammonia had disappeared. The solution was then filtered to remove any insoluble impurities and carbon dioxide passed through the dark-colored filtrate. After some time a reddish-yellow gelatinous substance was precipitated. This was filtered, washed, redissolved in dilute alkali and re-precipitated by carbon dioxide. When thus purified, it appeared as an amorphous, reddish-yellow powder. The yield was practically quantitative.

A Dumas nitrogen determination gave the following results:

0.15 gram of substance gave 34.8 cc. of nitrogen at 23° and 759 mm.

N	Calculated for	Found.
	$C_{10}H_6O_2N_4$. Per cent.	Per cent.
	26.17	26.11

The substance melts above 310° . It is insoluble, or very difficultly soluble in water, alcohol, benzol or the usual neutral organic solvents. It dissolves readily in dilute caustic alkalies and is reprecipitated from such solutions by dilute acids, preferably acetic, or carbon dioxide.

As a considerable quantity of this naphthotetrazine was desired, and as the yield of ethyl *m*-diaminometaphthalate was very poor, the 4,6-diformyldiaminoisophthalic acid was prepared, in the hope that the "Diformylanthranil" might be obtained, and this be allowed to react with ammonia.

4,6-Diformyldiaminoisophthalic Acid.



4,6-Diaminoisophthalic acid was boiled under a reflux condenser for some hours with a large excess of glacial formic acid. The diamino acid gradually went into solution, with formation of a dark-colored liquid. Upon cooling, yellowish, minute, needle-like crystals formed. These were filtered and washed with glacial formic acid and finally with water. Upon distilling off the excess of formic acid from the mother-liquor another crop of crystals were obtained. These were darker in color, however, and probably less pure. A nitrogen analysis on the pure substance gave the following result:

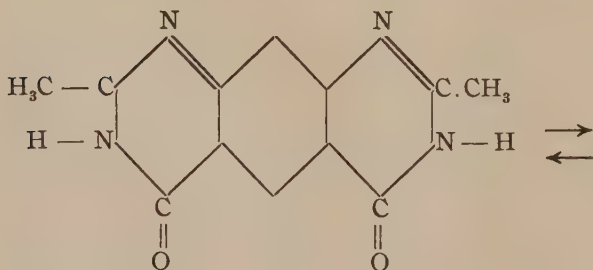
Wt. of sample = 0.1501 gram. Vol. of nitrogen at $19^\circ.5$ and 757.5 mm. = 14.8 cc.

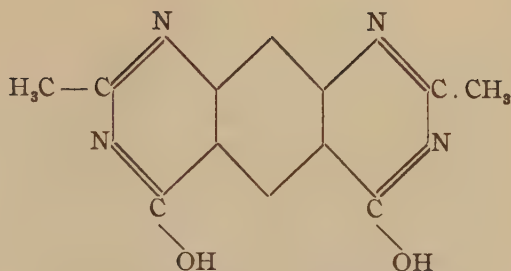
N	Calculated for	Found.
	$C_{10}H_8O_6N_2$.	Per cent.
	Per cent.	Per cent.
	11.11	11.27

The pure compound is practically infusible. It melted only when the capillary tube was held in the Bunsen burner. It is insoluble in water, soluble in alcohol from which it does not crystallize nicely, and is best purified by re-dissolving in formic acid and allowing to crystallize. It is soluble in alkalis or carbonates and is reprecipitated from such solutions as an amorphous product by acidification with acetic or hydrochloric acids. Boiling with acetic anhydride gradually dissolved the compound. On cooling, a white, crystalline compound formed, which proved to be "diacetanthranil." In other words, acetic anhydride failed to form the desired "diformylanthranil," the formyl radicle being replaced by the acet group.

It was also attempted to prepare this acid by oxidation of the 4,6-diformyl-*m*-xylol. In this case, however, a violent reaction took place when permanganate was added, showing that the formyl or aldehyde groups also underwent oxidation. The compound isolated was not studied further.

2,8 - Dimethyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine
(*2,8-dimethyl-4,6-dihydroxy-1,3,7,9-naphthotetrazine*).





Ethyl diacetyl-*m*-diaminometaphthalate was heated with an excess of alcoholic ammonia in a sealed tube for five hours at 200°. When cold, the tube was filled with a dark-colored residue. This was filtered from the excess of alcoholic ammonia, dissolved in dilute potassium hydroxide solution, filtered again to remove insoluble impurities, and the filtrate saturated with carbon dioxide. After some time a dark-colored, gelatinous precipitate formed. This was filtered out, washed with hot water, redissolved in caustic potash solution and re-precipitated by carbon dioxide. Dried in constant weight at 110°, the substance appeared as a pale yellow amorphous powder, melting above 300°.

A Dumas nitrogen determination gave the following figures:
0.0571 gram of sample gave 11.7 cc. of nitrogen at 20° and 756 mm.

	Calculated for $C_{12}H_{10}O_2N_4$. Per cent.	Found. Per cent.
N	23.1	23.3

The pure compound is practically insoluble in all of the ordinary organic solvents, such as alcohol, benzol, ether and chloroform and permits of purification only by repeated solution in dilute caustic potash and subsequent reprecipitation by carbon dioxide.

This same naphthotetrazine was also obtained by allowing a dilute ammonia solution to act on the diacetanthranil. Di-

acetantranil was added in small portions to a dilute solution of ammonia water. As no reaction took place in the cold the mixture was heated.

The diacetantranil, at first insoluble, suddenly went into solution, and at the boiling temperature, a yellowish crystalline substance separated out. This was filtered, dissolved in dilute potassium hydroxide solution and reprecipitated by carbon dioxide. The precipitate dried at 110° appeared as a pale yellow powder, identical with the one obtained from the condensation of ethyl-*m*-diacetyldiaminometaphthalate with alcoholic ammonia. It is practically insoluble in all neutral organic solvents and melts above 300° . An analysis to determine its nitrogen content obtained the following figures:

0.0833 gram substance gave 17.3 cc. of nitrogen at 26° and 758 mm.

	Calculated for $C_{12}H_{10}O_2N_4$ Per cent.	Found. Per cent.
N	23.1	22.9
C	59.5	59.68
H	4.13	4.24

Diacetyl-m-diaminometaphthalisoamylamide,



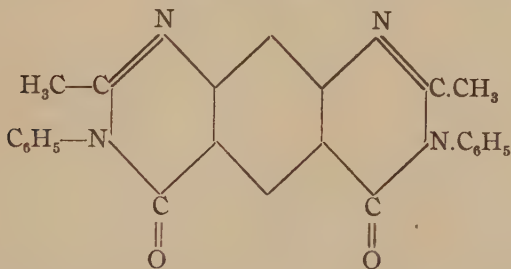
Ethyldiacetyl-*m*-diaminometaphthalate was heated with an excess of isoamylamine. A clear solution was obtained and upon evaporation of the isoamylamine over a free flame a white substance was obtained. This dissolved readily in alcohol and could be crystallized in fluffy white needles from dilute alcohol. A Dumas nitrogen determination gave the following results:

0.150 gram substance gave 18 cc. of N at 21° and 758 mm.

N	Calculated for $C_{22}H_{14}O_4N_4$ Per cent.	Found. Per cent.
	13.4	13.6

The pure substance melts at 189°.6 (corr.). It is insoluble in water, but dissolves in alcohol, benzol and the other organic solvents. Contrary to the isoamylamide made by Nelson⁴ from ethyldiacetyl-*p*-diaminoterephthalate, it is not changed to the naphthotetrazine when boiled with caustic alkalies. The same compound was also obtained when the diacetanthranil was heated with isoamylamine.

2,8 - Dimethyl - 3,7 - diphenyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine,



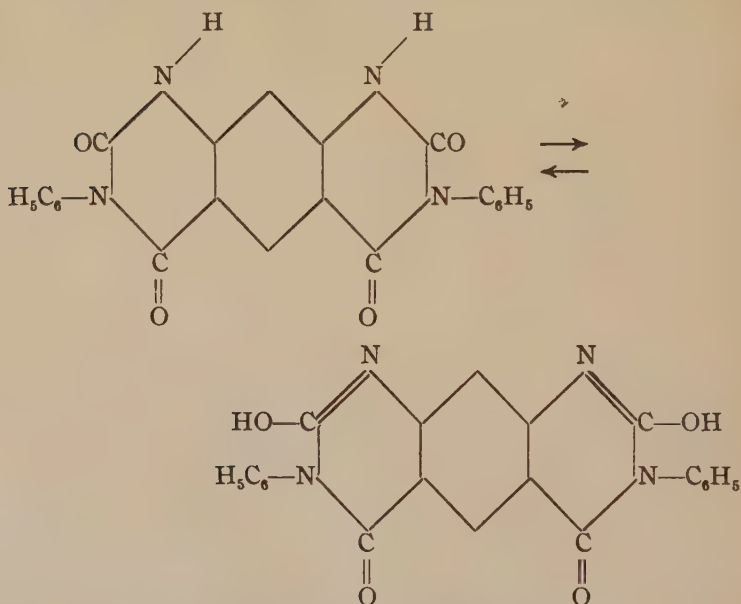
Ethyl diacetyl-*m*-diaminometaphthalate and aniline were heated together at ordinary pressure and for two hours at 200° in a sealed tube, but in either case no change could be observed. When, however, the diacetanthranil was boiled for about 15 minutes with an excess of aniline under a reflux condenser, white needle crystals separated from the solution on cooling. These were filtered off, washed with acetic acid and then with water, and crystallized from a large amount of alcohol. In this way white, fluffy needles, melting at 315°, were obtained. A nitrogen analysis gave the following figures:

0.1514 grams of sample gave 17.7 cc. of N at 13° and 770 mm.

N	Calculated for	Found.
	$C_{24}H_{18}O_2N_4$. Per cent.	Per cent.
	14.21	14.00

This is evidently the diphenylnaphthotetrazine sought, as the nitrogen percentage in the corresponding amide is only 13.02. The compound is insoluble in water or acetic acid and also in benzol, ligroin and ether. It can be crystallized, however, from large quantities of alcohol.

3,7 - Diphenyl - 2,4,6,8 - tetraketo - octahydro - 1,3,7,9 - naphtho - tetrazine. (3,7 - Diphenyl - 2,8 - dihydroxy - 4,6, - diketote - trahydro-1,3,7,9-naphthotetrazine.



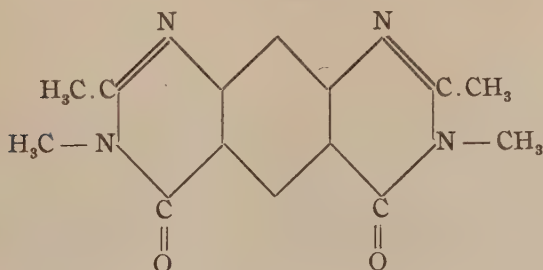
Ethyl diphenyluraminometaphthalate and aniline were heated together for some time at ordinary pressure but no change was evident. When, however, the phenyluramino ester was heated with aniline in a sealed tube for six hours at 225° ,

the desired reaction took place. After cooling upon opening the tube it was found that considerable decomposition had taken place. The product was boiled with glacial acetic acid and filtered. Upon cooling large brownish-green crystals were deposited out of the solution. These were filtered from the mother liquor and washed with glacial acetic acid and water. They apparently contained acetic acid of crystallization as they still smelled strongly of acetic acid, even after thoroughly washing with water, and became pulverulent upon drying at 110° . This powder was dissolved in dilute caustic potassium solution and reprecipitated from this solution by carbon dioxide. After filtering, washing, and drying it appeared as a colorless, amorphous product which melted above 300° . An analysis of its nitrogen content showed the following figures: 0.15 gram of substance gave 18.1 cc. of N at 18.5° and 768.5 mm. pressure.

	Calculated for $C_{22}H_{14}O_4N_4$. Per cent.	Found. Per cent.
N	14.07	14.066

The purified substance is apparently insoluble in water, alcohol or benzol. It is soluble in glacial acetic acid and in dilute potassium hydroxide solution, from which solution it can be reprecipitated either by carbon dioxide or by acidification with dilute acetic acid.

2,3,7,8 - Tetramethyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphtho - tetrazine.



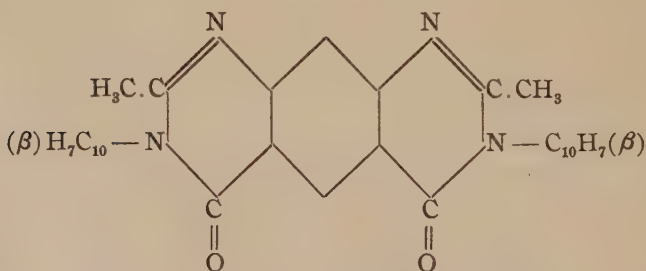
Diacetantranil (1 molecule) was heated with an aqueous methylamine solution. (2 molecules + 25 per cent. excess). As the temperature of the solution increased the anthranil gradually went into solution, forming a clear, yellow liquid, and on boiling for a few moments, a white crystalline compound separated. This was filtered and washed with hot water and recrystallized from a large volume of boiling alcohol. In this manner it forms in nice long, white needles, which melt above 350°.

A Dumas nitrogen determination on 0.1656 gram of substance gave 29.8 cc. of N at 17.5° and 764 mm. pressure.

	Calculated for $C_{14}H_{14}O_2N_4$. Per cent.	Found. Per cent.
N	20.74	20.9

This naphthotetrazine is insoluble in water, benzol, ether, chloroform and most of the usual organic solvents. It is soluble, however, in large quantities of boiling alcohol.

2,8 - Dimethyl - 3,7 - di - B - naphthyl - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.



Ethyl diacetyl-*m*-diaminometaphthalate was heated for some time with β -naphthylamine. The mass gradually became liquid and darkened considerably, leaving a pasty substance from which nothing definite could be isolated. When diacetantranil, on the other hand, was heated with β -naph-

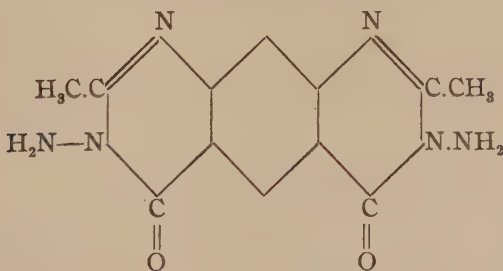
thylamine the mass became liquid and considerable frothing took place. After some time this ceased and the reaction product solidified. It was then removed, pulverized, and extracted with hot dilute hydrochloric acid and finally washed with water. A grayish-amorphous powder was the result. This powder was dissolved in a large quantity of alcohol. On cooling, needles of a grayish cast and showing fluorescence crystallized out. These were filtered, washed with alcohol, dried at 110° and analyzed for nitrogen with the following result:

0.15 gram of substance gave 15 cc. of N at 22° and 758 mm. pressure.

N	Calculated for $C_{32}H_{28}O_2N_4$.	Found.
	Per cent.	Per cent.
	11.24	11.3

The purified compound melts at 304° . It can be crystallized from a large volume of alcohol. The alcoholic mother liquor shows decided fluorescence. The compound is insoluble in water, benzol, ether and chloroform.

2,8 - Dimethyl - 3,7 - diamino - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.



This naphthotetrazine was readily obtained when one molecule of diacetanthranil was heated with two molecules plus a slight excess of 50 per cent. hydrazine hydrate solution.

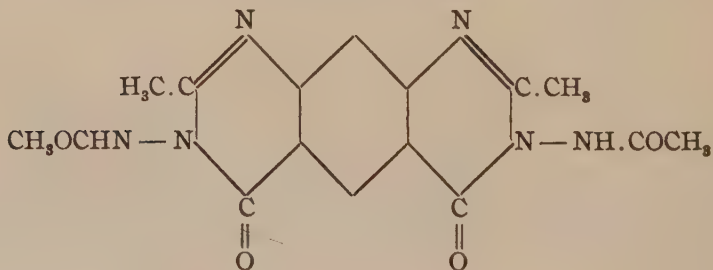
The hydrazine hydrate solution was put into about 25 cc. of water, and the anthranil added. Reaction did not take place in the cold, but on heating the mixture the anthranil gradually went into solution, forming a red colored liquid and at the boiling temperature the naphthotetrazine was precipitated in the form of beautiful, nacreous scales of a yellowish color. When cold the compound was filtered, washed with water, dried at 110° and analyzed without further purification.

A Dumas nitrogen determination gave the following result: Weight of sample = 0.1005 gram. cc. of N evolved = 28.2. $T = 24.0^{\circ}$. $P = 753$ mm.

	Calculated for $C_{12}H_{12}N_8O_2$. Per cent.	Found. Per cent.
N	30.9	31.15

The naphthotetrazine melts above 360° . It is insoluble in water, benzol, and several of the other organic solvents and only slightly soluble in alcohol. It dissolves in concentrated hydrochloric acid, from which it is precipitated on cooling as the hydrochloride. Acetic anhydride forms the acetyl amino derivative. It reacts with diacetyl succinic diethyl ester to form a condensation product containing two substituted pyrrole cycles. Treated with $NaNO_2$ in a hydrochloric acid solution it reacts with α - or β -naphthol to form red dye-stuffs.

2,8 - Dimethyl - 3,7 - diacetamino - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.



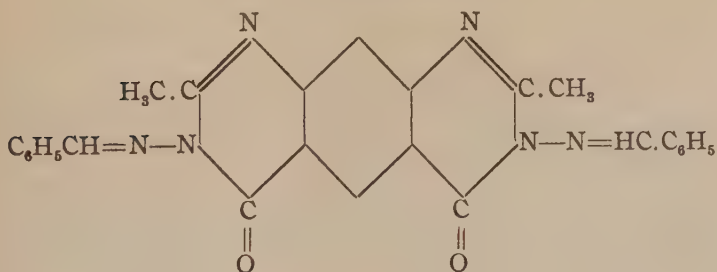
When the above naphthotetrazine was heated with acetic anhydride it gradually went into solution and upon concentrating small white needles separated. These were filtered and the excess of acetic anhydride removed with a small amount of carbon tetrachloride. Upon further concentrating the mother liquor another small batch of rather impure crystals was obtained. These were further purified by crystallization from large quantity of boiling alcohol in which they are fairly soluble. They melt above 360° . Upon analysis the following figures were obtained:

0.0733 gram of sample gave 15 cc. of N at 17.5° and 767 mm. pressure.

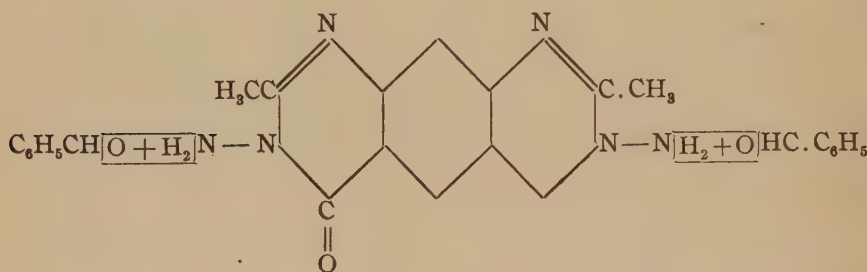
	Calculated for $C_{16}H_{16}O_4N_6$. Per cent.	Found. Per cent.
N	23.6	23.9

This indicates that only one hydrogen atom of the amino groups is replaced by the acetyl group. An attempt to prepare the tetracetyl derivative by further treating the diacetyl derivative with acetic anhydride was not successful. The diacetyldiamino-naphthotetrazine is insoluble in water, benzol, ether and chloroform. It is moderately soluble in alcohol but can be crystallized from large amounts of it.

2,8 - Dimethyl - 3,7 - diaminobenzylidene - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.



This compound was prepared from the corresponding diaminonaphthotetrazine by a condensation with benzaldehyde according to the following reaction.



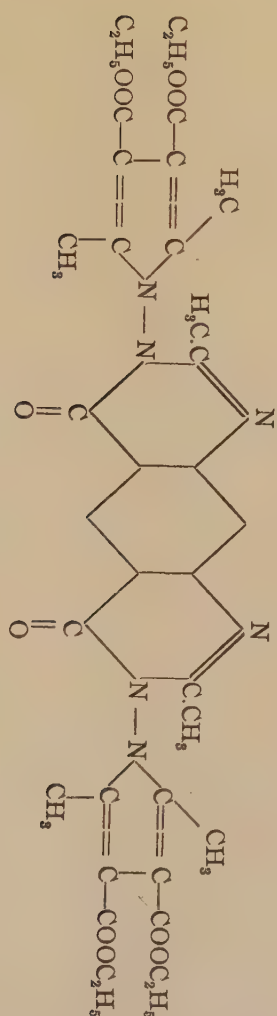
The diaminonaphthotetrazine was boiled for a few minutes in a test tube with an excess of benzaldehyde. It gradually went into solution with formation of a dark yellow colored liquid. Water condensed on the sides of the tube near the top, showing that a reaction had taken place. On cooling a granular yellow solid separated. This was extracted with boiling alcohol several times to remove all aldehyde. The compound melts above 350° and burned with difficulty. An analysis gave the following result:

0.15 gram of substance gave 25.2 cc. of N at 21° and 753 mm. pressure.

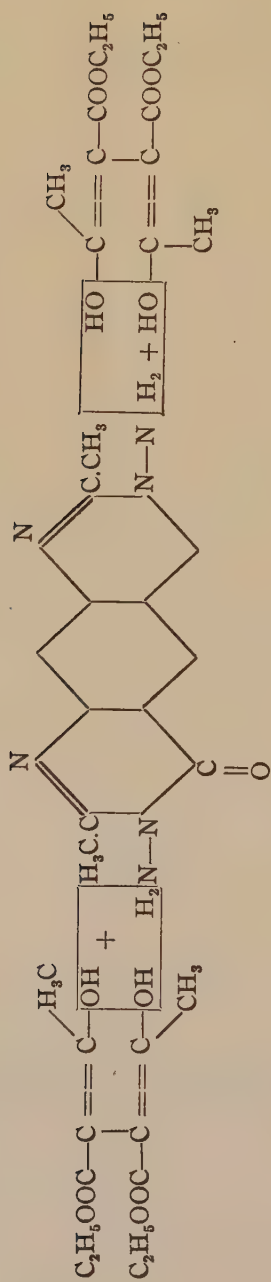
	Calculated for $C_{26}H_{20}N_6O_2$. Per cent.	Found. Per cent.
N	18.7	18.9

The compound is insoluble in all of the ordinary organic solvents, but is soluble in benzaldehyde, from which it separates in the cold as a granular solid.

2,8 - Dimethyl - 3,7 - di - (2,5 - dimethyl - 3,4 - dicarbethoxy pyrrole) - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.



This compound is formed by the interaction between the 2,8-dimethyl - 3,7 - diamino - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine and di-aceto succinic diethyl ester as shown below:

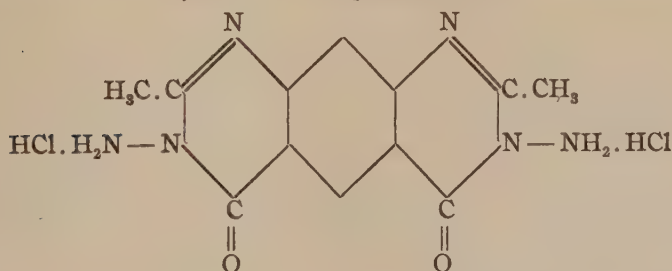


The 3,7-diaminotetrazine was boiled in glacial acetic acid solution under a reflux condenser with the calculated amount of diacetyl succinic diethyl ester for one hour. At first a vigorous reaction took place, but this gradually abated until at the end of one hour the solution was boiling quietly. The acetic acid was then evaporated to very low bulk and when cooled unchanged naphthotetrazine crystallized out. This was filtered out and the mother liquor diluted with water, causing the precipitation of a white, amorphous compound. On boiling the dilute acetic acid solution this dissolved and when cooled minute prismatic crystals separated. These were filtered and crystallized from alcohol. On addition of more water to the acetic acid mother liquor another batch of impure product was obtained. The compound as crystallized from alcohol melts at 268.2° (corr.).

A Dumas nitrogen analysis on 0.1507 gram of the substance gave 16.1 cc. of nitrogen at 22.5° and 765 mm. pressure.

N	Calculated for	Found.
	$C_{36}H_{40}O_6N_{10}$. Per cent.	Per cent.
	11.75	12.1

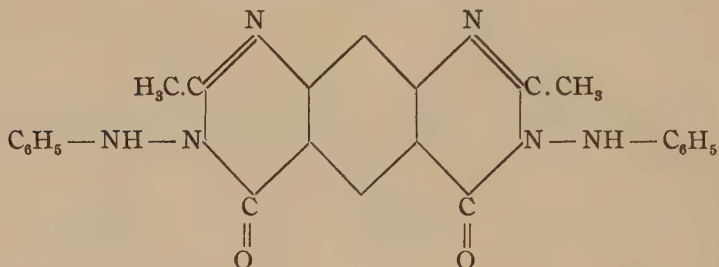
Hydrochloride of 2,8-dimethyl-3,7-diamino-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.



When the diaminonaphthotetrazine was boiled with a concentrated solution of hydrochloric acid it went into solution,

forming a clear colorless liquid. Upon concentration of the hydrochloric acid and cooling, white prismatic crystals formed which melted above 360° with decomposition and evolution of gas. These are evidently the hydrochloride of the diamino-naphthotetrazine as they are readily soluble in cold water. Upon addition of a little sodium carbonate to the aqueous solution effervescence takes place and the free diamino naphthotetrazine is precipitated.

2,8 - Dimethyl - 3,7 - diphenylamino - 4,6 - diketotetrahydro - 1,3,7,9-naphthotetrazine.

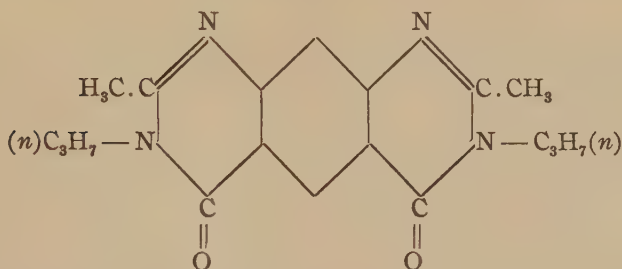


Diacetantranil was put into a beaker and covered with an excess of phenylhydrazine. A reaction took place immediately, accompanied by evolution of heat and upon further warming the mixture the reaction became quite violent. Upon cooling a granular compound separated. Alcohol was then added to the solution and the mixture boiled and filtered. The residue was again extracted with boiling alcohol until no more phenyl hydrazine could be detected in the alcoholic washings. This procedure gave rise to a nice, white granular compound, which apparently was insoluble in hot alcohol and was unmelted at 320° .

A Dumas nitrogen determination obtained the following figures:

0.15 gram of substance gave 26 cc. of N at 18° and 761.5 mm. pressure.

	Calculated for $C_{24}H_{20}O_2N_6$. Per cent.	Found. Per cent.
N	19.81	20.05
<i>2,8 - Dimethyl - 3,7, - dipropyl (n) - 4,6 - diketotetrahydro - 1,3,7,9 - naphthotetrazine.</i>		



This naphthotetrazine was obtained by allowing diacet-anthranil to react with propyl amine in an aqueous solution. The anthranil was introduced in the cold dilute propyl amine solution and gradually heated to boiling. As the temperature rose the anthranil dissolved forming a light yellow colored solution and on boiling the naphthotetrazine was thrown down in a somewhat flocculent amorphous form. This product was crystallized from dilute alcohol. It formed in glistening fluffy bunches of small needles.

A Dumas nitrogen analysis showed the following figures:

0.0903 gram of sample gave 13.2 cc. of N at 17° and 764 mm. pressure.

	Calculated for $C_{18}H_{12}O_2N_4$. Per cent.	Found. Per cent.
N	17.1	17.05

The pure compound softens slightly at about 180° and melts at 220°. It is insoluble in water but readily soluble

in alcohol. It is insoluble in benzol, ether and chloroform. It is best crystallized from dilute alcohol.

4,6-Diacetamino-m-toluic acid.



This acid was found in the acid mother liquor of the oxidation of 4,6-diacetylamino-*m*-xylol after the 4,6-diacetylamino isophthalic acid had been removed by addition of hydrochloric acid. It will be remembered that after filtering off the manganese dioxide, hydrochloric acid was added to the hot solution. This caused a flocculent precipitation of the isophthalic acid. The solution was then again filtered while still hot. From this filtrate when cold small colorless needles crystallized. It was at first supposed that this was some of the isophthalic acid which might have gone into solution in such a large volume of water as the crystals when filtered and dried showed a melting point of 272.4° (corr.). This was not the case, however, for a mixture of this compound with a sample known to be 4,6-diacetyldiamino isophthalic acid showed a melting point of 158° .

A Dumas nitrogen determination gave rise to the following result:

0.2003 gram of sample gave 19.7 cc. of N at 19° and 763.5 mm. pressure.

	Calculated for $C_{12}H_{14}O_4N_2$. Per cent.	Found. Per cent.
N	11.2	11.3

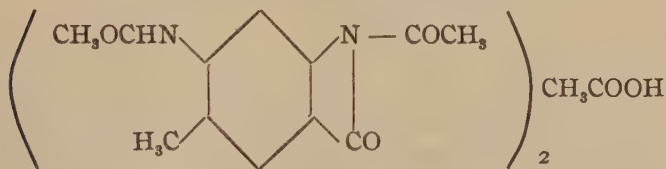
This is unquestionably the toluic acid, formed probably by incomplete oxidation of the corresponding xylol derivative.

Its formation was not observed in every instance. Usually

when the xylol derivative was oxidized in a flask provided with a return condenser instead of in a large dish by means of steam this compound could be isolated. Therefore it would seem that the oxidation is more complete when steam is passed through the solution while permanganate is being added.

The 4,6-diacetyl diamino toluic acid is only slightly soluble in water, but can be crystallized from alcohol or dilute acetic acid. From the former solvent it separates in fine glassy needles. The acid is easily soluble in dilute solutions of potassium or sodium hydroxide or carbonate and is reprecipitated in crystalline form from such solutions by acidification with hydrochloric acid.

4-Acet-amino-5-methyl-acetanthrnil.



This anthranil is obtained when the above acid is boiled for about 15 minutes with an excess of acetic anhydride under a reflux condenser. The solution darkened considerably on strong concentration and when cooling and scratching the sides of the beaker a yellowish-white crystalline compound separated. This was filtered and recrystallized from acetic anhydride. In this way a product was obtained which formed in small needles pseudo-white and melting at 166.2° (corr.) Peculiarly enough, however, when this compound was analyzed for its nitrogen value it always gave a figure which was too low for the nitrogen value calculated if it were a straight anthranil. As recrystallizations from acetic anhydride would not change the melting point a carbon and hydrogen analysis were also run and from the figures it appears that this anthranil exists combined with one-half molecule of acetic acid. That this is

the actual case was shown to satisfaction by just melting a small portion of the sample in a test tube over a small flame. A piece of blue litmus paper held over the top of the tube immediately became red, and the odor of acetic acid was distinctly noticeable. This acid is apparently held very strongly by the compound as it is retained even up to the melting point of the compound.

A Dumas nitrogen determination obtained the following figures:

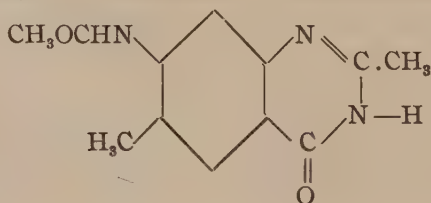
0.1500 gram of substance gave 14.4 cc. of N at 23° and 762 mm. pressure.

	Calculated for $C_{22}H_{28}O_8N_4$. Per cent.	Found. Per cent.
N	10.7	10.8
	Calculated Per cent.	Found Per cent.
C	59.5	59.6
H	5.3	5.2

In its other general properties this compound agrees closely with those of the other acet anthranils which have been prepared. It is hydrolyzed by boiling with water or alcohol and gives the corresponding diacetyldiamino toluic acid. It is soluble in ethyl acetate to some extent and can be crystallized from that solvent. It is likely, however, to partially hydrolyze so it is best obtained in a pure state by crystallizing from acetic anhydride.

Ammonia and primary amines condense with it to form the substituted methyl-acetamino quinazolines.

2,6 - Dimethyl - 7 - acetamino - 4 - ketodihydroquinazoline.



This compound is formed by the action of dilute ammonia water upon the above 4-acet-amino-5-methyl-acetantranil. No reaction took place in the cold when the substances were brought together, but on heating the anthranil gradually went into solution forming a clear yellow liquid and at the boiling temperature the quinazoline was precipitated.

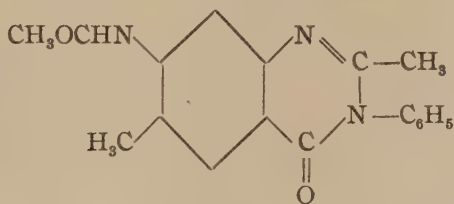
The solution was then concentrated on the water bath to drive off the excess of ammonia. The quinazoline formed in nice white needles which melted at about 330° .

A Dumas nitrogen determination on 0.1372 gram of substance gave 22.4 cc. of nitrogen at 23° and 760 mm. pressure.

	Calculated for $C_{12}H_{13}O_2N_3$. Per cent.	Found. Per cent.
N	18.18	18.4

The quinazoline is easily soluble in dilute solutions of potassium or sodium hydroxide and is reprecipitated from such solutions by acidification with dilute acetic acid.

2,6 - Dimethyl - 3 - phenyl - 7 - acetamino - 4 - ketodihydro-quinazoline.

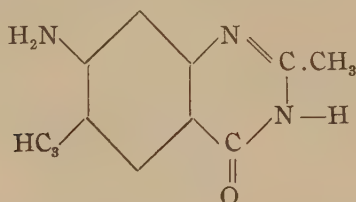


4-Acetamino-5-methyl-acetantranil was heated with an excess of aniline. On cooling the desired quinazoline separated. The excess of aniline was removed with dilute acetic acid and the product crystallized from large quantities of dilute alcohol. It melts at 271° (uncorr.). It forms in beautiful, glistening diamond shaped plates for which the following figures were obtained upon analysis of their nitrogen content:

0.15 gram sample gave 18 cc. of N at 16° and 752 mm. pressure.

	Calculated for $C_{18}H_{17}O_2N_3$. Per cent.	Found. Per cent.
N	13.68	13.75

2,6-Dimethyl-7-amino-4-ketodihydroquinazoline.



This quinazoline was obtained from the corresponding diacetaminoquinazoline by boiling for some few minutes with a 10 per cent. caustic potash solution under a reflux condenser. The alkaline liquid was then filtered and saturated with carbon dioxide. The amino quinazoline was precipitated as a colorless, flocculent compound which was unmelted at 300°. As only a small quantity of the compound was obtained it was deemed best to again dissolve it in caustic potash and reprecipitate with carbon dioxide and thus purify it instead of crystallizing from some solvent. The compound thus purified gave the following result for its nitrogen content:

0.0512 gram of sample gave 10 cc. of N at 21° and 769 mm. pressure.

	Calculated for $C_{10}H_{11}ON_3$. Per cent.	Found. Per cent.
N	22.22	22.4

This quinazoline is soluble in alcohol and also in dilute hydrochloric acid. Nitrous acid acts on it in acid solution giving a compound which when coupled with α -naphthol gives an intense orange dyestuff.

4-Acetylamino-6-nitroisophthalic Acid.

This acid had already been prepared by Errera and Maltese ⁽¹⁸⁾ by acetylating 6-nitro-4-amino-*m*-xylol and oxidizing the acetylated compound by potassium permanganate and allowing the reaction to become alkaline. In the course of this research it was found that if the oxidation was carried out in the presence of magnesium sulphate to keep the solution neutral, the yield of acetamino nitroisophthalic acid was increased. 6-Nitro-xylidine, prepared as already described, was boiled with an excess of acetic anhydride under a reflux condenser for about half an hour. At the end of that time the reaction product was poured into a large excess of water. The acetylated nitro xylidine which was precipitated was thoroughly triturated in a mortar several times to free it from acetic acid and acetic anhydride and finally thrown upon a filter and washed thoroughly. In this way a fairly pure product consisting of mono- and diacetyl nitro xylidine was obtained. Without further purification or separation of the two acetyl derivatives the mass was put into a large flask, fitted with a return condenser, a sufficient amount of magnesium sulphate added, and the mixture oxidized by successive additions of finely pulverized potassium permanganate. Enough permanganate was added so that a small portion when filtered still gave a decided pink color after boiling for about 30 minutes. A few cc. of alcohol were then added to the oxidation product to destroy all the permanganate and the mass filtered to remove the manganese dioxide. The clear filtrate was allowed to cool and any unchanged acetyl amino nitro xylol was re-

¹⁸ Errera and Maltese, *Gazz. chim. ital.*, **33**, 2287.

moved. The neutral solution was then concentrated strongly and made decidedly acid with hydrochloric acid. The 4-acetyl-amino-6-nitroisophthalic acid separated as an oil which quickly became granular and solid. It was then filtered and washed and dissolved in hot glacial acetic acid. On cooling the desired acid crystallized out in small opaque needles which melted with evolution of gas at 264° . On concentrating the mother liquor another crop of crystals, slightly impure, was obtained. This compound in all respects was similar to the one obtained by Errera and Maltese. It is insoluble in water, but can be crystallized from either alcohol or acetic acid. It is insoluble or very nearly so in benzol. On saponification with very dilute sulphuric acid the acet group is eliminated and 4-amino-6-nitroisophthalic acid is obtained.

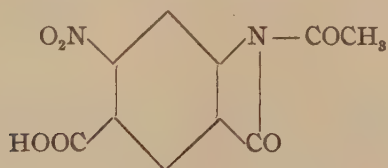
4-Amino-6-nitroisophthalic Acid.



The above acetylated acid was boiled for about thirty minutes with a 3 per cent. solution of sulphuric acid under a reflux condenser. At the end of that time the reaction product was poured into a large quantity of water. The desired amino acid was precipitated in a flocculent form. Upon crystallization from dilute acetic acid it appeared in small yellow nodules of a crystalline structure. This product also corresponded to the one obtained by Errera and Maltese. It melts with decomposition and evolution of gas at 280° . In some respects this acid is almost as unreactive as the 4,6-diaminoisophthalic acid. It was found that the nitro group was exceedingly difficult to reduce to the corresponding amino

as boiling with concentrated acids would eliminate one of the carboxyl groups giving the corresponding benzoic acids. An attempt to diazotize the amino group also was unsuccessful. The diazotization was tried in a sulphuric acid solution and also in a hydrochloric acid solution without success. Amyl nitrite in an absolute alcohol solution did not give any better results. It was observed that when the 4-acetyl-amino-6-nitroisophthalic acid was saponified with 50 per cent. sulphuric acid, no free amino nitro acid could be obtained, but instead a mixture of 4-nitroanthranilic acid and 4-amino-2-nitrobenzoic acid. This was due to the elimination of one of the carboxyl groups from the isophthalic acid by the action of the strong acid. Saponification with alkali had the same effect.

3-Carboxy-4-nitroacetanthranil.



Since in both 4-amino-6-nitroisophthalic acid and 4-acetyl-amino-6-nitroisophthalic acid there is an amino group in a position *ortho* to a carboxyl group it was decided to see whether these compounds would behave like anthranilic acid, and give an acetanthranil when boiled with an excess of acetic anhydride. This proved to be the case 4-acetyl-amino-6-nitroisophthalic acid was boiled with an excess of acetic anhydride over a reflux condenser for about two hours. The acid quickly went into solution with formation of a light yellow colored liquid which darkened somewhat during the boiling. The solution was concentrated and allowed to cool. Groups of small yellowish-white crystals separated after some time. These were filtered out, washed with acetic anhydride and then carbon tetrachlor-

ide to remove the excess of anhydride and dried at 110° . They melted at 274.4° (corr.).

A Dumas nitrogen determination gave the following result:

0.1500 gram of sample gave 14.8 cc. of nitrogen at 22° and 763 mm. pressure.

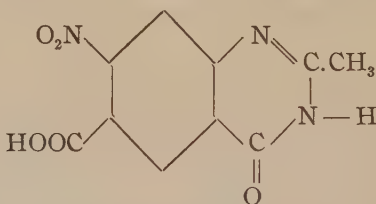
	Calculated for $C_{10}H_8O_6N_2$. Per cent.	Found. Per cent.
N	11.2	11.23

On boiling with water or alcohol, the acetantranil breaks at the $C = O$ cycle and regenerates the acetyl acid. It is



soluble in ethyl acetate, and can be crystallized from this solvent. A partial hydrolysis, however, is apt to occur. The acetantranil is best purified by recrystallizing from a small amount of acetic anhydride. 4-Amino-6-nitroisophthalic acid gave the same anthranil on treatment with acetic anhydride.

7 - Nitro - 6 - carboxyl - 2 - methyl - 4 - ketodihydroquinazoline.



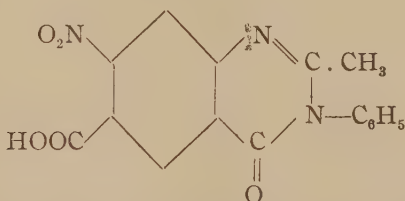
This quinazoline was obtained when a dilute solution of ammonia water was allowed to act on the above acetantranil. The acetantranil was added to a solution containing ammonia water and boiled for a few minutes and finally taken to dryness on a water bath to insure a complete reaction. The residue was then taken up with a dilute solution of potassium hydroxide and filtered to remove any impurities. Hydrochloric acid was carefully added to the filtrate until slightly acid. The

precipitated quinazoline was filtered, washed and crystallized from boiling water. It separated in nice, colorless needles which melted above 300° .

0.1505 gram of substance gave 22.1 cc. of nitrogen at 20° and 766 mm. pressure.

	Calculated for $C_{10}H_7N_3O_6$. Per cent.	Found. Per cent.
N	16.8	16.93

7 - Nitro - 6 - carboxyl - 2 - methyl - 3 phenyl - 4 - ketodihydro-quinazoline.



3-Carboxyl 4 nitroacetanthranil was boiled with a slight excess of aniline. On cooling, a dilute solution of acetic acid was added. The precipitated quinazoline was filtered, washed and crystallized from alcohol. It forms in beautiful yellow prisms which melt at 315° .

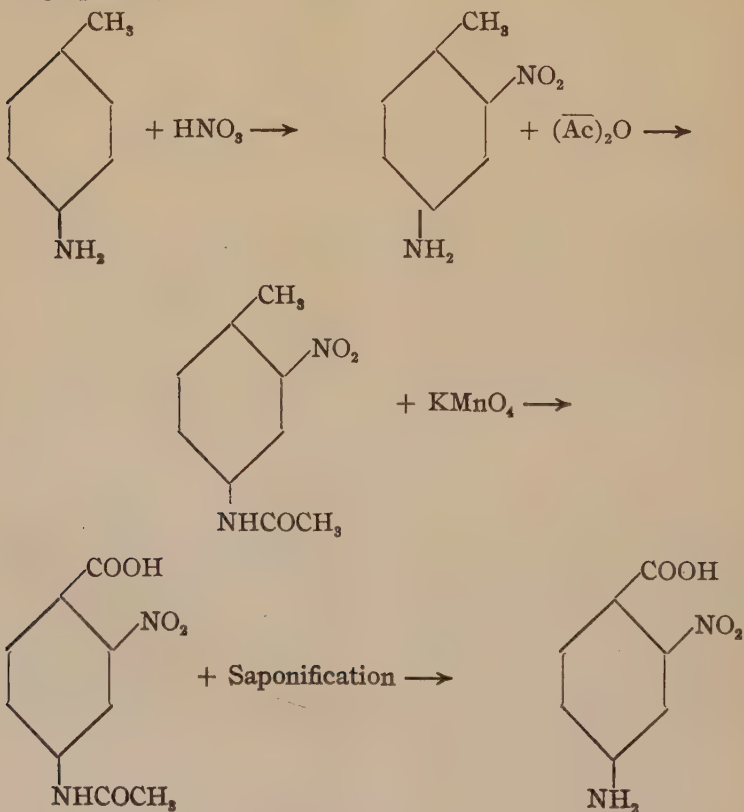
A nitrogen analysis gave the following figures: Wt. of sample 0.1502 gram. Vol. of N = 17.4 cc. $t = 20^{\circ}$. $p = 769$ mm.

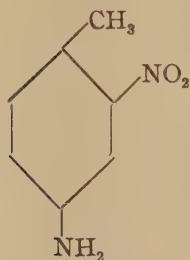
	Calculated for $C_{15}H_{11}N_3O_6$. Per cent.	Found. Per cent.
N	13.4	13.41

As has already been stated elsewhere it was found that when 4-acetyl amino-6-nitroisophthalic acid was boiled with 50 per cent. sulphuric acid, not only the acetyl group, but also a carboxyl group was eliminated. This gave rise to a mixture of 4-nitroanthranilic acid (m. p. 264°) and another acid which melted at $241-2^{\circ}$. It was found difficult to separate this

mixture. Crystallizing from acetic acid seemed to be the best way, the 4-nitroanthranilic being more insoluble and leaving the other acid in the mother liquor. Upon concentration of this a reddish-yellow product crystallized out in the form of needles. Repeated crystallizations failed to raise the melting point. A nitrogen analysis gave a figure corresponding to 2-nitro-4-amino benzoic acid. Acetic anhydride gave a colorless compound which melted at $217-8^{\circ}$ and which did not possess any properties common to acetantranil.

It was therefore decided to prepare some 2-nitro-4-amino benzoic acid from *p*-toluidine. The scheme followed out can be graphically shown as follows:



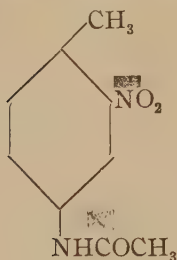
2-Nitro p-Toluidine.

This compound was prepared from *p*-toluidine precisely as described by Nölting and Collin (B. 17, 263).

100 grams of *p*-toluidine were dissolved in 2000 grams of concentrated sulphuric acid. The mixture was cooled below 0° by ice and salt, and so arranged that it could be mechanically stirred. A mixture of 75 grams of nitric acid (1.48 sp. gr.) and 300 grams of concentrated sulphuric acid was then also cooled below 0° and allowed to drop slowly into the toluidine-sulphuric acid. During the nitration the temperature was never allowed to rise above zero. It ranged in general from -3° to -1° .

After all of the nitro-sulphuric acid had been added, stirring was continued for about an hour and the reaction product poured into six liters of ice water at the end of that time. Here also care was taken not to allow the temperature to get above 20° – 25° .

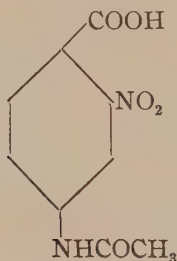
The solution was then diluted with cold water to about 15–20 liters and neutralized with sodium carbonate. The precipitated nitro compound was filtered, washed thoroughly and allowed to dry. A single crystallization from alcohol gave a pure product melting sharply at 77° . The yield was almost quantitative, and no formation of any isomeric nitro compound was observed.

2-Nitro-p-acettoluid.

This compound was readily obtained by adding the above nitrotoluidine to an excess of acetic anhydride. Reaction took place in the cold, with formation of considerable heat. The reaction product was boiled for a few minutes to complete the acetylation and then poured into water. The insoluble product which separated out was triturated thoroughly in a mortar with several portions of water, to free it from acetic acid and anhydride and crystallized from dilute alcohol. It forms in yellowish crystals melting at 148.5° (corr.). An analysis gave the following:

0.1498 gram sample gave 18.9 cc. at 20° and 764 mm. pressure.

	Calculated for $C_9H_{10}N_2O_3$. Per cent.	Found. Per cent.
N	14.43	14.51

2-Nitro-4-acetylamino Benzoic Acid.

2-Nitro-*p*-acet toluid was oxidized in a flask provided with a reflux condenser with a slight excess over the calculated amount of potassium permanganate in the presence of magnesium sulphate to keep the reaction neutral. The permanganate was added in small portions to the boiling solution from time to time. After all had been added, the boiling was continued until all color of the permanganate had disappeared. The entire oxidation required about two hours. The hot solution was then filtered, and the filtrate concentrated strongly and allowed to cool. A small amount of unoxidized compound separated out, and was filtered off. The solution was then acidified with hydrochloric acid. This precipitated the desired 2-nitro-4-acetamino benzoic acid in a granular form. Crystallized from alcohol it appeared as small needles of a yellowish-white color, and melting at 219° (corr.).

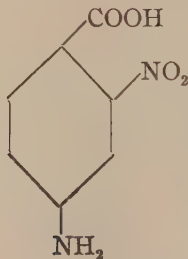
A Dumas nitrogen determination obtained the following result:

0.1500 gram of substance gave 16.2 cc. of nitrogen at 21° and 761 mm. pressure.

	Calculated for $C_8H_8O_5N_2$ Per cent.	Found. Per cent.
N	12.5	12.31

To all appearances this acid was identical with the one obtained by acetylating the acid derived in the saponification of 4-acetylamino-6-nitroisophthalic acid with 50 per cent. sulphuric acid. Dilute sulphuric acid, or better, a 10 per cent. solution of potassium hydroxide saponified the acetyl group and yielded the free,

2-Nitro-4-amino Benzoic Acid.



This acid melts at 239.5° (corr.) and is crystallized best from dilute acetic acid. It forms in beautiful bronzy scales which possess a high lustre. It is slightly soluble in cold water, more readily so in hot water, and is easily soluble in glacial acetic acid or alcohol. It possesses a very sweet taste.

An analysis obtained the following results:

0.1505 gram of substance gave 21.0 cc. of nitrogen at 25° and 761 mm. pressure.

	Calculated for $C_7H_9O_4N_2$ Per cent.	Found. Per cent.
N	15.38	15.5
C	46.15	46.3
H	3.29	3.48

When heated with an excess of propyl aldehyde on the water bath under a reflux condenser, a reaction took place giving rise to a dark colored, syrupy mass which after distilling off the remaining aldehyde became solid. This mass was then dissolved in alkali and reprecipitated by dilute acetic acid. It formed a rather gelatinous material which was difficult to purify. When dry a yellowish-red amorphous powder resulted, which was not further investigated.

RÉSUMÉ.

1. 6-Nitroxylidine (1,3,4) is easily reduced to the corresponding diamido derivative, which, upon acetylation and subsequent oxidation yields 4,6-diacetdiaminoisophthalic acid.

2. This acid, when saponified with concentrated hydrochloric acid, loses its acetyl groups and forms the hydrochloride of 4,6-diaminoisophthalic acid, which in turn yields the free diamino acid.

3. Ethyl or methyl alcohols in the presence of dry hydrochloric acid gas, esterify the diacetyl derivative of the above acid giving respectively: Ethyl- and methyl-*m*-diaminometa-phthalate the acetyl group also being eliminated during the esterification.

4. Small quantities of the acid ester are also formed during esterification, accompanied by ethyl-2,4-diaminobenzoate, formed by the elimination of one of the COOH groups from the isophthalic acid.

5. Ethyl *m*-diaminometaphthalate forms ethyl *m*-diphenyl-uraminometaphthalate with phenylisocyanate, and this in turn condenses with primary amines, as aniline, to form the corresponding naphthotetrazines.

6. Ethyl *m*-diaminometaphthalate can be acetylated by both mono and bibasic anhydrides.

7. Ethyl diacetyldiaminometaphthalate condenses with primary amines to form naphthotetrazines or intermediate amides.

8. Ethyl *m*-diaminometaphthalate condenses with formamide to yield a naphthotetrazine.

9. Acetic anhydride acts on 4,6-diaminoisophthalic acid or its acetyl derivative, eliminating two molecules of water and forming the dilactam of diacetyl-*m*-diaminoisophthalic acid.

10. This dilactam condenses with primary amines to form the corresponding naphthotetrazines. The condensation takes place very much more readily than when the ester is used.

11. In the oxidation of 4,6-diacet diamino-*m*-xylol to the corresponding isophthalic acid, a small amount of the corresponding toluic acid was isolated in the mother liquors.

12. The diacetdiaminotoluic acid when boiled with acetic anhydride yields the corresponding methyl-, diacetamino-anthranil.

13. This anthranil reacts with primary amines forming substituted quinazolines of the 2,6-dimethyl-7-acet-amino type.

14. 4-Amino-3-nitroisophthalic acid or its acetyl derivative when boiled with acetic anhydride yields 3-carboxy-4-nitro-acetanthranil.

15. This anthranil condenses with primary amines to form quinazolines of the 2-methyl-7-nitro 6-carboxy type.

16. When 4-acetylamino-6-nitroisophthalic acid is saponified with very dilute sulphuric acid, the free amino acid forms. When strong acid is used, CO_2 is eliminated and a mixture of 4-nitroanthranilic and 2-nitro-4-amino benzoic acids result.

17. 2-Nitro-4-amino benzoic acid was also made from 2-nitro *p*-toluidine by acetylation and oxidation and subsequent saponification of the acetyl derivative.

18. This acid possesses a sweet taste, and reacts with propyl aldehyde, giving a dark-colored amorphous powder which has not been further investigated.

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BIOGRAPHICAL.

Alfred Hemmer Kropff was born in New York City, on January 2, 1887. He entered Columbia University in the fall of 1902, and, after taking the academic course for one year, entered the School of Chemistry in the fall of 1903. From this department he graduated in 1907, receiving the degree of Bachelor of Science. During the academic year 1907-1908 he did research work in organic chemistry for the degree of Master of Arts, which was granted in 1908. During 1908-1909 he continued this organic research work, and studied for the degree of Doctor of Philosophy.

In conjunction with Professor H. C. Sherman he published a paper on "The Calorific Power of Petroleum Oils and the Relation of Density to Calorific Power," in the *Journal of the American Chemical Society*, 30, 1626.

In conjunction with R. A. Gortner he published a paper on "Peptic Digestion in Pure Solutions of Acid Salts" (in press).

